DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

29 July 1998

Dr. Barrett N. Fountos
U.S. Department of Energy
Office of International Health Programs
EH-63/270CC
19901 Germantown Road
Germantown, MD 20874-1290

Dear Dr. Fountos:

I have received a call from Mr. T. Fox who, on behald of Mr. Hawkins, requested copies of the three quarterly progress reports from the Columbia University. Being that you are the Project Officer on our Interagency Agreement, I am sending these reports to you to be in compliance with the Agreement. Let me know when you receive them, please.

Sincerely yours,

Ihor J. Masnyk, Ph.D.
Project Officer
NCI-DOE Interagency Agreement

DEPARTMENT OF HEALTH & HUMAN SERVICES

National Institute of Health
National Cancer Institute
OEM, RCB, TCS
Executive Plaza South, Room 603
Phone: 496-8620 FAX 402-6699

Memorandum

Date: July 15, 1998

From: **Dr. Ihor J. Masnyk**
Project Officer

Subject: Technical Report

To: **Mr. Richard Hartmann**
Contracting Officer

Contractor: **Columbia University**

Contract number: **N02-CB-77032**

Reporting Period Covered: 04/01/98-06/30/98

Type of report: **Quarterly Progress Report**

I have reviewed the above mentioned technical progress report

✓ The report is satisfactory

___ The report is unsatisfactory, see comments below

COMMENTS:

Signature of Project Officer

Columbia School of Public Health

CSPH

July 14, 1998

Dr. Ihor Masnyk
Project Officer, Radiation Effects Branch
Division of Cancer Biology
National Cancer Institute
Executive Plaza North, Room 530
6130 Executive Blvd.
Rockville, MD 20852

RE: SUPPORT AND MANAGEMENT FOR THE PROJECT: "EFFECTS OF THE CHERNOBYL ACCIDENT ON THYROID CANCER AND LEUKEMIA/LYMPHOMA" CONTRACT BETWEEN NATIONAL CANCER INSTITUTE AND THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK

Dear Ihor:

With respect to the above, enclosed please find the Third Quarterly Progress Report for the period April 1, 1998 - June 30, 1998.

We welcome any comments or suggestions.

Sincerely,

Geoffrey R. Howe, Ph.D.
Professor and Head
Division of Epidemiology

Enclosures

SUPPORT AND MANAGEMENT FOR THE PROJECT:
"EFFECTS OF THE CHERNOBYL ACCIDENT ON THYROID CANCER AND LEUKEMIA/LYMPHOMA"
CONTRACT BETWEEN NATIONAL CANCER INSTITUTE AND THE TRUSTEES OF
COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK
QUARTERLY PROGRESS REPORTS, APRIL 1, 1998 - JUNE 30, 1998

1. INTRODUCTION

The third quarter of the contract focused on the overall impressions and recommendations suggested by those who traveled to Belarus and Ukraine in early 1998 regarding the studies in those countries together with preparations for and execution of the Columbia team on-site visit to Belarus and Ukraine in May/June. Prior to the second site visit meetings were held both at Columbia and NCI regarding issues and problems arising from the initial site visits.

2. April 28, 1998 Meeting at Columbia University:

On April 28, 1998, a meeting was held at Columbia University of all Columbia team members who participated in the February 1998 trip to Ukraine and Belarus, with the exception of Dr. Geard (Biological Dosimetry). The trip participants in attendance were Professor Burch (Epidemiology and Fieldwork), Dr. Fink (Clinical Laboratory Management and Quality Control), Dr. Heitjan (Data Management and Biostatistics), Dr. McConnell (Endocrinology) and Dr. Reiss (Hematology and Pathology). Other members of the Columbia team who were also present included Dr. Geoffrey Howe (Epidemiology), Dr. Greenebaum (Cytology and Pathology), Ms. Sally Hodgson (Program Coordinator), and Drs. Medvedovsky and Worgul. The primary purpose of the meeting was both to discuss overall impressions of the February trip with Dr. Howe who had just returned to work and to prepare for the meeting to be held on the following day in Washington, D.C. with NCI staff (see Section 3 below).

The problem of how to best communicate Columbia's recommendations to investigators in Ukraine and Belarus via the contract with the NCI was discussed together with overall impressions of the

work to date in the studies, preparations for the upcoming trip of certain members of the Columbia team to the study areas, and training (including the identification of potential trainees from Ukraine and Belarus).

3. April 29, 1998 Meeting at NCI:

The following members of the Columbia team attended a meeting at NCI: Dr. Geoffrey Howe, Professor David Burch, Drs. Daniel Fink, Ellen Greenebaum, Daniel Heitjan, Robert McConnell and Robert Reiss. The members from NCI and their consultants included Drs. Ihor Masnyk, Bruce Wacholz, Gil Beebe, Stuart Finch, Jack Robbins with Drs. Randy Brill and Everett Mincey via a teleconference call. NCI provided the Columbia team with updated information regarding the studies and in particular discussed issues and recommendations made by the Columbia team as a consequence of the February trip to Belarus and Ukraine.

In brief, participants at the meeting discussed the following issues and recommendations:

A. Communication between Belarus/Ukraine, Columbia and NCI:

- Copies of all communications should be sent to Dr. Masnyk and the Columbia University Chernobyl Study Center (e-mail: sk683@columbia.edu);
- NCI will accelerate transfer of information from study sites to the Columbia team.

B. Future Travel:

- Possibility that one individual from Columbia could travel to study sites for extended periods;
- Possibility that Everett Mincey stay in Belarus/Ukraine for minimum 2-3 months;
- It would be more effective if trips were made by smaller groups representing one or two disciplines which could spend more time in direct contact with their opposite members, rather than the large group meetings which currently occupy a substantial portion of trips.

C. Training:

- Columbia to propose personnel from Belarus and Ukraine for training at Columbia (or elsewhere in the U.S);
- Columbia team members would prepare outlines of proposed training schedules for individuals in their areas of expertise.

Specific scientific problems and issues relevant to each individual study in Belarus/Ukraine were also discussed all of which are subsequently addressed in the trip reports (Appendix 1) and the summaries of these reports (see Section 5 of this report) for those individuals who visited Belarus and Ukraine in May/June, 1998.

4. MAY 18, 1998 TO JUNE 7, 1998 TRIP TO UKRAINE AND BELARUS

Members of the Columbia team (Dr. Geoffrey Howe, Professor David Burch, Drs. Daniel Fink, Ellen Greenebaum, and Robert McConnell) together with NCI personnel and consultants (Drs. Ihor Masnyk, Bruce Wacholz, Gil Beebe, André Bouville, Randy Brill, Stuart Finch, and Herman Mitchell) traveled to Ukraine and/or Belarus for an on-site visit. The trip provided the NCI the opportunity to introduce a member of the team (Ellen Greenebaum) to her scientific counterparts in the thyroid cancer studies in Ukraine and Belarus. The focus of this second trip by the Columbia team together with members of NCI and their consultants was to update the American scientists with progress to date in the three studies and allow the Columbia team to continue their interaction with their counterparts in the studies so that the ongoing needs of the studies could be recognized, discussed and responded to. The Columbia scientific personnel were thus able to offer concrete suggestions to facilitate the execution of the studies.

Upon their return to the USA, members of the Columbia team prepared individual trip reports (see Appendix 1) with each individual report reflecting the expertise of the scientist and including his/her

suggestions as they relate to his/her specialty. A brief summary of the observations and recommendations suggested by the relevant participants from Columbia follows.

5. STUDY OF LEUKEMIA AMONG CLEAN-UP WORKERS: SUMMARY OF INDIVIDUAL TRIP REPORTS

A. Professor J. David Burch, Epidemiology and Fieldwork Procedures

Professor Burch reviewed study design, fieldwork procedures and progress to date with Dr. Natalia Gudzenko, Head of the Epidemiology Group at the Research Centre for Radiation Medicine, subsequent to a trip to Dnipropetrovsk oblast which has been chosen as a "pilot" oblast, to assess ongoing fieldwork. Problem areas within this oblast particularly and the overall study were identified. He held further meetings to discuss fieldwork in the entire cohort with Dr. Gudzenko.

As a result of these meetings, Professor Burch made the following observations and recommendations:

I. ***Dnipropetrovsk oblast:***

- Immediate initiation and careful documentation of follow-up and pilot testing of study procedures in this oblast should be implemented as soon as possible.

ii. ***Passive follow-up:***

- The use of the Ministry of Internal Affairs, benefits file from Ministry of Chernobyl Affairs, and lifetime events files should be pursued in order to obtain access to such records for Phase II.

iii. ***Pathological review of retrospective diagnosis of leukemias, lymphomas and related disorders:***

- Professor Burch and Dr. Gudzenko are presently focusing on the ongoing planning and implementation of procedures for a review panel to assess the viability of clinical and biological material in Ukraine together with diagnostic review of this material for

retrospective cases diagnosed with leukemias, lymphomas and related disorders (see Appendix 2 of this report for Draft Protocol) for this review.

More details of Professor Burch's recommendations are included in his trip report (Appendix 1).

B. Dr. Geoffrey R. Howe, Epidemiology

Two days were spent in discussions with Drs. Natalia Gudzenko and Irena Gubina and with Dr. Vadim Chumak and others involved in dosimetry. Professor Burch was also present at these discussions. Topics discussed included the state of the pilot project in Dnipropetrovsk, follow-up procedures for the Phase II study, methods of and training for computerized probabilistic record linkage and the protocol for the pathology review developed by Professor Burch and Dr. Gudzenko. Other topics included the integration of dosimetry and epidemiology, in particular, how doses estimated by various means could be used in the final analysis.

In addition, a short visit was paid to Dr. Cortushin's institute to discuss more details of the Chernobyl State Registry and, again, the topic of computerized record linkage.

The following primary observations/recommendations were made:

- There is an urgent need to develop facilities to conduct computerized probabilistic record linkage in several institutions in Ukraine including the Institute of Radiation Medicine, the Chernobyl State Registry, and possibly several other sources of information.
- The most cost-effective way of introducing the necessary skills in computerized record linkage would be for Dr. Howe to conduct a small training session in Kiev which could be attended by those who would conduct such linkages from the various institutions involved.
- The record linkage software could be purchased "off the shelf" at a modest price which could be utilized more or less directly with the various data bases involved.
- It is essential that the epidemiologic and dosimetric aspects of the study be fully integrated, and there needs to be continuous contact between the epidemiologists and dosimetrists.

- Consideration should be given to further supporting the development of the so called "fuzzy set" doses, since these are the only ones which will be available for the entire set of cases and subcohort members.
- Work should be initiated on the development of appropriate statistical techniques for incorporating the various types of dose measurements into an appropriate risk analysis methodology.

More details of Dr. Howe's recommendations are included in his trip report (Appendix 1).

6. STUDY OF THYROID CANCER AND OTHER THYROID DISEASES IN UKRAINE: SUMMARY OF INDIVIDUAL TRIP REPORTS

A Professor J. David Burch, Epidemiology and Fieldwork Procedures

A series of meetings were held with Dr. Anna Derevyanko, Head of the Epidemiology Group at the Institute of Endocrinology and Metabolism and Dr. Valery Tereshchenko, Vice-Director of the Thyroid Study in Ukraine, during which Professor Burch reviewed study procedures (i.e., ascertainment of the cohort, fieldwork and the in utero study).

As a result of these meetings, Professor Burch made the following observations and recommendations:

I. ***Ascertainment and establishment of cohort and follow-up:***

- Linkages between other files such as that of the Ministry of Internal Affairs (passport office) should be undertaken as soon as possible;
- For continued follow-up of recruited cohort members it is essential that cohort members be asked to provide further identifying information about their parents, close friends, or other possible contact persons;

- Thank you letters must be sent to recruited cohort members who have participated in screening and questionnaire administration.

ii. ***Fieldwork:***

- Questionnaires need amendment, i.e., determination of who responded to what questions, assessment of quality of information by interviewers;
- Determine cut-off age of child at time of screening to enable interviewing of knowledgeable parent or other person;
- Use of video technology to train interviewers to be assessed.

iii. ***Documentation of study procedures:***

- In progress to date in the pilot Ivankiv raion it is apparent that there has been no documentation in the field as to procedures followed and subsequent consequences. It is absolutely essential that all study procedures in progression of the study from cohort identification, recruitment, screening, to follow-up be carefully documented.

iv. ***Coding and data entry:***

- It is absolutely essential that coding manuals be compiled as soon as possible for all questionnaires and forms to be completed in the study and that coding staff be trained using this manual.
- Once the coding manuals have been written and data coded, data entry must ensue as quickly as possible.

v. ***In utero study:***

- Linkage of Institute of Pediatrics file with dose measurement file would be improved by utilizing probabilistic record linkage system.

More details of Professor's Burch's recommendations are included in his trip report (Appendix 1).

B. Dr. Geoffrey R. Howe, Epidemiology

Dr. Howe visited the Endocrinology Institute in Kiev in conjunction with the visit by NCI staff, consultants and other Columbia team members for a four-day period. Discussions were primarily held with Dr. Derevyanko and members from the data coordinating center. Issues discussed included fieldwork, follow-up and the necessity for probabilistic record linkage.

The following primary observations/recommendations were made:

- As with the leukemia study, there is an urgent need for computerized probabilistic record linkage, which could be addressed in the same training session as proposed for the leukemia study.
- Rather than exhaustively trying to trace the untraced members of the initially selected cohort of 20,000, it may be more cost effective, and present no threat to validity, to simply recruit the more easily traced members of the remaining 60,000 members of the cohort.
- A case-control within a cohort or case-cohort design would be much more cost effective, just as powerful and as equally unbiased as the full cohort design.
- Considerable caution needs to be utilized before making any decision as to a preliminary statistical analysis based on a small number of thyroid cancer cases, since such an analysis could be very misleading and could threaten the credibility of the study.
- Specific recommendations regarding details of the fieldwork were also proposed and are summarized in Dr. Howe's trip report.

More details of Dr. Howe's recommendations are included in his trip report (Appendix 1).

C. Dr. Ellen Greenebaum, Cytology/Pathology

Dr. Greenebaum's comments are confined to cytology and pathology, emphasizing cytology. She met primarily with Dr. Yu M. Bozhok, Head of Cytology Laboratory, and four other cytologists: Drs. Khorozhenko, Kulinichenko, Uscimenko and Zelinskaya regarding cytology and pathology.

As a result of these meetings and observing cytological and pathological procedures, Dr. Greenebaum made the following observations and recommendations:

I. ***Definition of diagnostic criteria:***

- Create written criteria for specimen adequacy, diagnostic criteria and instructions for form completion.

ii. ***Monitoring cytology/pathology:***

- Create log of cohort cases, fine needle aspiration biopsy diagnosis and histology diagnosis directly in the laboratory and DCC.
- Establish system for performing and documenting secondary review of case studies when initial diagnosis is "non-informative."
- Establish and document when slides are discarded (prior or subsequent to recording number of slides).
- Criteria for determining surgical intervention need to be changed to reflect actual procedures (i.e., ***all*** detected nodules are aspirated).

iii. ***Performance of FNAs by endocrinologists/sonographers:***

- Determine the frequency with which FNAs are performed by endocrinologists rather than sonographers.
- Based on specimen adequacy rates, determine if endocrinologists require additional training or credentials or if all aspirates should be done by sonographers.

More details of Dr. Greenebaum's recommendations are included in her trip report (Appendix 1).

D. Dr. Robert McConnell - Endocrinology

Dr. McConnell reviewed clinical operations regarding endocrinology, meeting primarily with Drs. Bogdonova, Bozhok and Terekova.

As a result of these meetings together with reviewing and observing clinical procedures, Dr. McConnell made the following observations and recommendations:

- Although considerable progress has been made since the last visit in February, and a respectable number of cohort subjects has been identified, the "no show" rate is quite high and the delay in processing laboratory specimens is a drag on progress.

- The need for an incentive for subjects to continue with the project is a recurring theme. A lottery might work, with several cohort members winning a token gift every day.

- It should be firmly established that the FNA biopsy is done on the same day as the ultrasonogram, since we could begin losing patients who cannot return for a follow-up visit.

- Urine for iodine should be collected at the time of the screening procedure and not brought from home.

- All "suspicious" nodules regardless of size should have an FNA biopsy at the discretion of the sonographer or endocrinologist. Even if we stick to the protocol (Section 5.4.1 of the Operations Manual states that, in patients over 12 years of age, only nodules larger than 1 cm should be biopsied), most nodules over 5 mm in diameter eventually may be sampled anyway. Not allowing the physicians to exercise clinical judgment could result in unnecessary tension. If it is decided to sanction biopsy of the smaller nodules, the Operations Manual will require amendment.

- After consulting with the people at the NIH, we will need to make a decision about continuing to perform thyroglobulin assays, which Dr. Ephstein wishes to stop doing.

- Although Dr. Ephstein is of the opinion that blood calcium levels should only be done fasting, it is unreasonable to expect patients to fast all morning and sometimes late into the afternoon waiting for screening to be completed. Blood should be obtained for calcium whether the subject has eaten or not and an appropriate notation made in the record.

- We need to meet Dr. Cherniv, a pathologist, who receives specimens from patients older than 30 years of age.

- Periodic visits to monitor operations at mobile sites should become part of our regular "routine."

More details of Dr. McConnell's recommendations are included in his trip report (Appendix 1).

E. Dr. Daniel Fink - Clinical Laboratory Management/Quality Control

Dr. Fink met primarily with Dr. Epshtein, Director of the Central Laboratory, Institute of Endocrinology and Metabolism. The discussions focused on laboratory issues and quality control.

As a result of these discussions, Dr. Fink made the following observations and recommendations:

I. ***Screening process:***

- It was agreed that the screening process will be modified to collect blood calcium even if the cohort member is not fasting.

ii. ***Testing protocol:***

- After considerable discussion it was agreed that Drs. Fink, Mincey, McConnell and Robbins will review this issue.

iii. ***Hormone/antibody testing:***

- No hormone or antibody testing has been performed as of now for cohort members. The current plan is to begin testing in September, 1998. It is recommended that testing must be initiated as soon as possible and it must keep pace with the screening process.

iv. ***Quality control:***

- Dr. Fink brought quality control literature from the U.S. for Dr. Epshtein and the basic concepts of this scientific endeavor were discussed.
- Dr. Epshtein seemed enthusiastic about the issue of quality control and it was agreed that he would initiate a program of this type as soon as possible.
- Dr. Epshtein is eager to receive unknown specimens from an external source and it was agreed that Dr. Fink will try to send specimens of this type from Columbia prior to his next visit to Ukraine.

More details of Dr. Fink's recommendations are included in his trip report (Appendix 1).

7. STUDY OF THYROID CANCER AND OTHER THYROID DISEASES IN BELARUS: SUMMARY OF INDIVIDUAL TRIP REPORTS

A. Professor J. David Burch - Epidemiology and Fieldwork

The ascertainment and follow-up of the cohorts (including the in utero cohort) and fieldwork procedures were the primary focus of the meetings Professor Burch had with Dr. Elena Buglova, Head of the Epidemiology Group, and her two colleagues, Drs. Ludmila Kul'kova and Alexander

Skalizhenko at the Institute of Radiation Medicine and Endocrinology together, with Mr. Artur Kuvshinnikov, Head of the Data Coordinating Center and Drs. Gil Beebe and Herman Mitchell.

As a result of these meetings, Professor Burch has made the following observations and recommendations

i. ***Ascertainment and establishment of cohort including follow-up***:

- Continued linking of the dose measurement file with the Chernobyl Registry and files from other data sources including the Bureau of Addresses/Ministry of Internal Affairs, Office of Technology and Ministry of Emergencies is essential.
- For continued follow-up of recruited and screened cohort members it is essential that thank you letters to these individuals be sent as soon as possible.

ii. ***Fieldwork:***

- Invitation letters should be more specific about what is required of the subject, e.g. fasting blood sample, necessity of interviewing or having questionnaires completed by knowledgeable surrogates for those who were children.
- Questionnaires should be changed in order to determine who responded to different questions (if any), and assessment of quality of information given at interview should be assessed by interviewers.

iii. ***Documentation of study procedures:***

- It is absolutely imperative that all study procedures ranging from identification of the cohort, tracing, recruitment, screening to follow-up be carefully documented and entered on the computer in an administrative file so that response rates, for example, can be instantly available. Because this area has been somewhat neglected it was difficult to determine exactly the current status of the cohort.

iv. ***Coding and data entry:***

- It is absolutely essential to develop as soon as possible a practical coding manual with do's and don'ts for the completion of all forms and questionnaires in the study. This manual should be used in conjunction with the training of coders who will further code questionnaires and forms prior to data entry. Data entry should keep pace with completion of coding of all forms.
- The problems associated with lack of quality control and quality assurance would be somewhat alleviated once a coding manual and training of staff using this document is instituted and coding/data entry together with data tabulations are instituted.

v. ***In utero study:***

- Following completion of the data entry of eligible births from a file containing all births in Belarus 1986/1987 the record linkage between this eligible birth file and the dose measurement file (and with other identifying files such as the Bureau of Addresses/Ministry of Internal Affairs) would be facilitated by the utilization of probabilistic record linkage as proposed by Dr. Howe.

More details of Professor Burch's recommendations are included in his trip report (Appendix 1).

B. Dr. Ellen Greenebaum, Cytology/Pathology

Dr. Greenebaum's comments are confined to cytology and pathology, emphasizing cytology. Dr. Greenebaum met primarily with Drs. Yelena Kapanovitcha and Dmidchik, Head of the Cytology Laboratory.

As a result of these meetings and observing cytological and pathological procedures, Dr. Greenebaum made the following observations and recommendations:.

i. ***Definition of diagnostic criteria:***

- Create written criteria for specimen adequacy, diagnostic criteria and instructions for form completion.

ii. ***Monitoring cytology/pathology:***

- Create log of cohort cases, fine needle aspiration biopsy (FNA) diagnosis and histology diagnosis directly in the laboratory and DCC.
- Establish system for performing and documenting secondary review of case studies when initial diagnosis is "non-informative."
- Establish and document when slides are to be discarded (prior or subsequent to recording number of slides).
- Criteria for determining surgical intervention need to be changed to reflect actual procedures (i.e., ***all*** detected nodules are aspirated).

iii. ***Performance of FNAs by endocrinologists/sonographers:***

- Determine the frequency with which FNAs are performed by endocrinologists rather than sonographers.
- Based on specimen adequacy rates, determine if endocrinologists require additional training or credentials or if all aspirates should be done by sonographers.

iv. ***Aksakochina:***

- Clarify role of Aksakochina in sonographic and FNA evaluation/re-evaluation.

More details of Dr. Greenebaum's recommendations are included in her trip report (Appendix 1).

C. Dr. Robert McConnell - Endocrinology

Dr. McConnell, in a series of meetings with Drs. Y. Dimidchik, A. Romanovsky and Rzhentsky, reviewed and observed clinical endocrinological operations.

As a result of these meetings, Dr. McConnell made the following observations and recommendations:

- Although the clinical screening is moving ahead at a steady pace, the bottleneck which has developed in the flow of data between the Dispensary and the DCC is threatening the entire project.

- Unlike the operations in Kiev, where a cytopathologist immediately reviews the FNA biopsy slides, the sonographers cannot be sure that they have an adequate specimen. Dr. Gapanovich, who is based at Dimidchik's Thyroid Surgery Center, works at the Dispensary part time and examines the slides late in the day. The sonographers could be taught to review slides, obviating the need for a cytopathologist to be in attendance. This would also be a useful skill for the mobile teams to have because, unlike the Ukraine, the Belarussians feel comfortable with the concept of doing FNA biopsies "on the road."

- The sonographers are aggressively pursuing small nodules, as they are in Kiev. If we support this practice, Section 5.4.1 of the Operations Manual will need modification.

- A means to translate between the "old" WHO classification of goiter and the "new" system will be required. This should not be too difficult and Dr. McConnell will discuss it with Jack Robbins.

- As in the Ukraine, direct observation of the mobile operations should be encouraged.

- Dr. Yuri Dimidchik, who has succeeded his father as Head of the Thyroid Surgery Center, is developing a "power base" of his own and we should cultivate a good relationship with him.

More details of Dr. McConnell's recommendations are included in his trip report (Appendix 1).

D. Dr. Daniel Fink - Clinical Laboratory Management/Quality Control

In meetings with Dr. Petrenko, Dr. Fink focused on the testing protocol, including hormonal/antibody testing, equipment and quality control.

As a consequence of these discussions, Dr. Fink made the following observations and recommendations:

i. ***Testing protocol:***

- After considerable discussion it was agreed that Drs. Fink, McConnell, Mincey, and Robbins should review this issue.
- For urinary iodine more data must be collected because there is considerable year to year variation in individual cohort members and in the average values by oblast for the cohort members.

ii. ***Hormone/antibody testing:***

- Testing is progressing slowly, blood and urine have been collected on approximately 1550 different cohort members in 2692 screening visits but only approximately 600 hormone tests have been completed. This process must be accelerated.
- The relocation of the laboratory is going to significantly delay hormone testing and the elimination of this backlog. RIA reagents may, in fact, expire unused if the delivery plan is not accelerated as soon as possible.

iii. ***Quality control:***

- Literature on quality control in the USA was provided to Dr. Petrenko by Dr. Fink and the basic concepts of this process was reviewed with the former. Dr. Petrenko is enthusiastic and informed Dr. Fink that he would establish a similar quality control program.
- Dr. Petrenko is eager to receive unknown specimens from an external source and Dr. Fink agreed to send to Dr. Petrenko such specimens from Columbia prior to his next visit to Belarus.

iv. ***Equipment:***

- The Abbott IMX broke during the last day of the meetings and the gamma counter interface has never been completely fixed. In regard to this problem, Dr. Fink recommended that a permanent mechanism for getting maintenance performed must be established and these instruments must be repaired.

More details of Dr. Fink's recommendations are included in his trip report (Appendix 1).

8. Training:

One trainee, namely Dr.Sergey Sholom, has been identified during the three-month period and brought to the U.S. for training. Dr.Sholom is a dosimetrist who is spending three weeks with Dr. Ed Haskell, one of the Columbia subcontractor's at the University of Utah, working in the area of electron paramagnetic resonance of teeth. This technique, which is regarded by Dr. Chumak, the primary dosimetrist in the leukemia study, as providing the "gold standard," obviously will play an important role in the study, even only in terms of validating doses made by other means. A description of the work to be undertaken by Dr. Sholom is included in Appendix 3.

The Columbia team is also in the process of developing outline proposals for training in their own areas of expertise. An example of such an outline prepared by Dr. Heitjan is included in Appendix

4. The objective is to prepare a series of such training proposals which could then be evaluated by NCI staff and consultants and will provide a "catalog" which should provide a clearer guide to our colleagues in Ukraine and Belarus as to the sort of training which might be available.

One specific proposal for training during the upcoming three-month period is that proposed by Dr. Howe in computerized probabilistic record linkage. These techniques will be essential in carrying out both leukemia and thyroid studies. The failure to match records from Dr. Likhtarev's dose file to the Chernobyl State Registry (success rate of about 25%) illustrates the necessity for having available more sophisticated approaches to linkage than have been tried to date. An outline of what is proposed follows.

The training session would be held at Dr. Cortushin's institute and would be attended by those who would actually carry out the linkages, i.e., statistical and data processing professionals. Presumably, representatives would attend from the Institute of Radiation Medicine, the Institute of Endocrinology, Dr. Cortushin's institute, possibly the Oncology Institute and any other agency which might provide databases to which cohort records need to be linked. Participants from Belarus could also participate or the session could be repeated in Minsk. The training team would consist of two members, namely, Dr. Howe and a Russian-speaking computer programmer from North America who is familiar with the concepts and practice of record linkage. The basic theory of record linkage would be covered by Dr. Howe in a series of informal seminars; there is no need for this to be taught at a very sophisticated level since the basic principles are readily understood and should be adequate for the task. The programmer would bring with him copies of software routinely used for computerized record linkage in Canada (either Statistics Canada or the Ontario Cancer Registry, both of which have such packages available). The North American programmer would demonstrate the practical details of using the system and there would be hand-on opportunities for those attending from Ukraine to work with the programs. There should be no problem with the use of the Cyrillic language in such linkage applications, since all characters are treated equally in record linkage and, internally, Cyrillic characters are simply stored as special keyboard characters.

The plan is to leave copies of the appropriate software with the various institutions involved so that it will be routinely available to them in the future. Ideally, such a training session would take place in conjunction with the next planned visit to Kiev in the fall, provided everything could be put into place by then. However, it may be necessary to wait until the new computer equipment is functional at Dr. Cortushin's institute.

9. Other Ongoing and Future Activities:

We anticipate that a number of the Columbia team will participate in the planned visit to Ukraine/Belarus in the fall. Since this will be the third visit involving Columbia team members, who now are acquainted with their corresponding colleagues in those states, such a visit should provide an opportunity for further detailed interaction in the various areas of expertise. The visit could also be used to conduct a training session in computerized probabilistic record linkage as described above and possibly for a further visit to Dnipropetrovsk oblast by a small group to provide a final evaluation of the conduct of the pilot leukemia study provided, of course, this is acceptable to the Ukrainian investigators.. In addition, Dr. Reiss, our hematologist, has volunteered to visit a number of hematological hospitals in Ukraine to assist with the evaluation of the appropriateness of the material for the pathology review. Professor Burch will continue to work on further development of the protocol for that review and assist with the necessary logistical planning; his experience in conducting a centralized pathology review of brain tumor material for an international study at the International Agency for Research on Cancer in Lyon last year should be very helpful in delineating some of the practical aspects of the review.

Dr. Heitjan and Howe will start working on the development of appropriate statistical techniques for incorporating the various measures of dose, with their varying measurement error structures, into an appropriate risk analysis methodology. This should help to identify areas where, for example, more data will be required in order to define the appropriate measurement error correction methodologies.

With respect to dosimetry, we anticipate having some input into the further development of the methodology for developing the "fuzzy set" dosimetry and Dr. André Bouville has outlined areas in which our dosimetrists, Drs. Haskell and Straume could contribute.

We are hoping that suitable candidates for training in some other areas may be identified during the coming three-month period and that plans be initiated for carrying out such training.

We anticipate that Dr. Fink will participate with Drs. McConnell, Mincey and Robbins in re-evaluating the required laboratory procedures in the thyroid studies. He also plans to send test specimens for blind evaluation in thyroid laboratories as a measure of quality control and hopes to enroll the laboratories in a proficiency program such as CAP.

Dr. Geard, our biological dosimetry expert, has been conducting work in the area of assessment of chromosomal changes in the lymphocytes of liquidators, an integral part of dose reconstruction for exposed clean-up workers. Evaluations of fluorescence in situ hybridisation [FISH] studies of radiation induced chromosomal changes indicated uncertainties as to whether chromosomes were involved randomly or non-randomly in aberration formation. Concern for the role of FISH biodosimetry in dose reconstruction along with some mechanistic interest prompted an extensive evaluation of all chromosome specific radiation studies. These concerns were shared by other investigators.

A review has been prepared which includes recommendations for use in chromosome biodosimetric investigations. This has been submitted to the International Journal of Radiation Biology. The title page and abstract are appended (Appendix 5).

In concert with the collation of all epidemiological and scientific –medical documents related to the Chernobyl incident ,an effort has been made to collect reports involving chromosomal changes. To

date all reports in English have been obtained and all those reports in Russian are being obtained from the Library of Medicine. Initial evaluations will be undertaken with our language proficient support staff, with full translations if desirable. Emphasis will be placed on those reports which include quantitative information to aid in the chromosome biodosimetry program.

Finally, work has continued and will continue during the next three months in several miscellaneous areas:

- Dr. Kokoreva continued translating documents and questionnaires from Belarus and Ukraine. Her translation was reviewed by Dr. Zablotska prior to duplication and circulation to relevant Columbia team members.

- Dr. Lydia Zablotska and Ms. Sally Hodgson, Program Coordinator, continue with the literature search and establishment of an in-house library. As questionnaires, protocols and articles are brought back by our investigators and translated, they are added to the library for open access to our team members.

  Work on the staff directory continues as well as a graphic representation of interactions between various personnel. Standardized spelling of the English transliteration of Russian names remains problematic.

- Ms. Sally Hodgson is in the process of projecting year one balances. Because this study was slow in beginning, it is anticipated that the remaining balance, except for salary monies, will be significant and plans for proposing training related activities are underway.

APPENDIX 1

Individual Trip Reports for Columbia Scientific Personnel Traveling to Ukraine and Belarus

TRIP REPORT

J. DAVID BURCH
EPIDEMIOLOGY AND FIELDWORK

Visit to Kiev, Ukraine - May 18, 1998 to June 7, 1998

I. STUDY OF LEUKEMIA AND OTHER HEMATOLOGICAL DISEASES AMONG CLEAN-UP WORKERS IN UKRAINE FOLLOWING THE CHERNOBYL ACCIDENT

A. Visit to Dnipropetrovsk Oblast

① Background: Prior to the plenary session and meetings with Drs. Beebe, Howe and other NCI staff and consultants, a group of investigators from Ukraine together with myself and Drs. Finch and Masnyk traveled to the oblast of Dnipropetrovsk in order to familiarize ourselves with study procedures being followed in the field. The Ukrainian investigators traveling with us included Drs. Bebeshko, Dyaghil and Gudzenko.

The oblast of Dnipropetrovsk had been chosen by the Ukrainian investigators to implement and complete Phase 1 of the study in Ukraine The primary objectives of Phase 1 of the leukemia/lymphoma study in clean-up workers is to determine the feasibility of procedures to identify and follow-up the larger cohort and to assess the availability of the appropriate clinical records together with pre-treatment biological material for clean-up workers in order to determine leukemia/lymphoma disease status.

② Hospital Visits: During our two day stay in Dnipropetrovsk oblast the Ukrainian investigators took us to a number of area hospitals in the cities of Dnipropetrovsk and Kryvyi Rig including oblast, city and raion hospitals some of which specialized in treatment of hematological diseases of clean-up workers. At the latter institutions we were introduced to medical staff who were

responsible for the initial diagnoses and treatment of hematological diseases in clean-up workers residing in Dnipropetrovsk oblast at the local area.

At all the institutions visited our questions regarding case identification and possible follow-up procedures of clean-up workers were answered. However often elaborate and confusing explanations were given of the organization of the medical care system in Ukraine at the oblast, city and raion level.

③ Hospital Number 3: We visited a local area hospital (designated hospital number 3) which is a regional raion hospital in the sense that all clean-up workers in the immediate area attend the polyclinic at this hospital for their annual examination as part of the Ukrainian health care system's follow-up of clean-up workers. We were told that in this raion, for example, there were approximately 600 clean-up workers in total registered in the Chernobyl State Registry who attended the polyclinic for examination and that such attendance was 100 percent owing to the fact that most of the staff in this polyclinic had worked in the clinic for a number of years and personally knew the clean-up workers.

④ Oblast Hospital: At the major oblast hospital in the city of Dnipropetrovsk we again were introduced to medical staff from the highest administrative levels to the staff responsible for the diagnoses and treatment of clean-up workers attending the hospital. It was at this hospital that we were introduced to Dr. Tatiana Chekmareva who is responsible for the management of case identification and follow -up at the Dnipropetrovsk oblast level.

⑤ Present Status of Clean-Up Workers in Dnipropetrovsk Oblast: In discussions with Dr. Natalia Gudzenko and Dr. Tatiana Chekmareva it was determined that approximately 18,000 of the clean-up workers registered in the Chernobyl State Registry who first worked at Chernobyl between 1986 and 1990 are currently resident in Dnipropetrovsk oblast.

⑥ Follow-up of the 18,000 Clean-up Workers: During the past year approximately 14,000 clean-up workers attended their local polyclinics in Dnipropetrovsk oblast for their annual examination. For the remaining 4000 clean-up workers, approximately half of them had been examined during the past two years while 600 had not come for their annual examination for the last three years, 300 for the last four years, and another 600 for five years or more. Drs. Gudzenko and Chekmareva anticipated that the majority of the 2000 who had not been examined during the past two years will re-appear for their annual examination. On this basis, the medical examination system of clean-up workers in Dnipropetrovsk oblast has current medical and personal identifying information on approximately 85% of the cohort.

⑦ Pilot Project to Trace and Examine Clean-up Workers Lost to Follow-up: During our visit to the Dnipropetrovsk oblast registry the pilot project to trace and examine clean-up workers identified as lost to follow-up in Dnipropetrovsk oblast was discussed. Professor Burch and Drs. Beebe, Howe, Gudzenko and Chekmareva met subsequently in Kiev regarding the pilot study, the details of which are discussed in Section C 1.

⑧ Present Status of Clean-up Workers in Other Oblasts and City of Kiev: At the meeting at the Dnipropetrovsk oblast registry the possible ascertainment of the other members of the entire cohort of clean-up workers from the remaining oblasts and Kiev city was discussed. The general agreement among the Ukrainian investigators was that the follow-up of clean-up workers resident in the oblasts of Donetsk, Kharkiv and Sumskaya would probably be similar to that in Dnipropetrovsk. It was suggested however that this will not be the case for Kiev oblast and Kiev City. It was suggested that the successful maintenance of continued follow-up of clean-up workers by regular attendance at annual examinations in Donetsk, Dnipropetrovsk, Kharkiv, and Sumskaya oblasts may be partially due both to the stable nature of the populations in these oblasts and the stability of medical staff in these oblasts where there is a minimum of job turnover allowing the medical staff to become acquainted on a personal level with the clean-up workers. Furthermore, it was learned that for Kiev

oblast identical data was sent to the Chernobyl State Registry for two years but this has since been rectified.

SUGGESTION: It was suggested that the appropriate personnel in the other oblasts and Kiev City be contacted at an official level so that tabulations can be run in each oblast for clean-up workers not re-attending polyclinics for their re-examinations.

⑨ Overall Impressions of Trip to Dnipropetrovsk Oblast: I was very impressed with the enthusiasm and cooperation of the medical staff at oblast and raion hospitals and at area polyclinics. However, despite meeting a wide variety of medical personnel at various levels of case management at these facilities and familiarizing myself with regard to how clean-up workers are entered into the medical system I was disappointed that I did not see any real field work procedures taking place.

B. Plenary Session. May 20, 1998
Research Center for Radiation Medicine, Academy of Medical Sciences of Ukraine, Kiev

The plenary session was chaired by Dr. A. Romanyenko, Project Director. Heads of each sub-division in the project commented on their division's progress to date. Details of this progress are included in the progress report which was supplied at the session.

C. Meeting with Drs. Dyaghil, Gudzenko, Finch and Klimenko, May 21, 1998

① Diagnostic Review: I met with Drs. Dyaghil, Gudzenko, Finch and Klimenko to discuss the need to ascertain as soon as possible the extent to which biological material will be available for diagnostic assessment for cases with leukemias/lymphomas in Phase II of the study and to organize the procedures to be followed by a yet to be appointed panel of hematologists/pathologists to review retrospective diagnoses of such cases in the Ukraine. It is my understanding that once this panel has been appointed it is essential that they gain some experience working together as a cohesive group so that, if Phase II of the study is implemented, they can continue to review the diagnoses of cases with leukemias, lymphomas and related disorders as they emerge in the ongoing cohort study.

A direct result of the meeting was that Professor Burch and Dr. Gudzenko subsequently are preparing a draft protocol to be followed in initiating the pathological review process which includes suggestions from Drs. Beebe, Finch and Howe. A copy of this draft protocol will be included in the Columbia sub-contract third quarterly report.

② Brief Description of Draft Protocol for Pathological Review of Retrospective Diagnoses of Leukemias/Lymphomas in the General Ukrainian Population:

- A diagnostic review is planned by a panel of expert hematologists/pathologists of both deceased and alive patients with diagnoses of leukemias, lymphomas and/or related diseases chosen from the general population of the Ukraine;

- The general Ukrainian population has been chosen for the basis of this review on the assumption (confirmed by Drs. Dyaghil and Klimenko) that the general population diagnosed with these diseases is not treated any differently than clean-up workers diagnosed with the same diseases in terms of diagnostic procedures and medical treatment;

- A random sample of cases with diagnoses of leukemias/lymphomas and related diseases will be chosen from oblast and hematological clinics of the same oblasts and other areas to be included in Phase II of the study. The sample will be based on different diagnostic categories among male cases in the defined age group of 20 to 40 years of age between 1986 and 1990 so that age at diagnosis should be comparable to that for the cleanup workers. The number of required cases in each sub-classification was determined by Drs Dyaghil and Finch;

- Approximately 20 cases diagnosed with leukemia/lymphoma and related diseases for the period 1987 to 1997 will be chosen from each of the following oblasts and study areas:

Dnipropetrovsk, Donetsk, Kharkiv, Kiev, Sumskaya and Kiev city giving a total of 60 cases for review;

- All clinical records, laboratory reports, pre-treatment blood, bone marrow/tissue samples, stains etc. will be requested from the medical facility at which each case was diagnosed and will be sent to Kiev for review;

- As far as possible, all clinical and biological material for each case will be "blinded" in order to reduce any bias on the part of the diagnostic reviewer;

- The purpose of the review essentially is to determine the availability of clinical and biological material for cases diagnosed with leukemias/lymphomas and related diseases together with giving the review team some experience working together. The review will not be able to identify false negative cases but will be able to identify false positives;

- Once the review has been completed all clinical and biological material will be sent back to the originating medical facility;

- Professor Burch and Dr. Gudzenko will take responsibility for the further development of the review protocol in collaboration with the hematologists involved and will organize and manage the review process itself which is tentatively planned for no later than January 1999;

- Membership of the review panel should be determined no later than the end of August, 1998 and it is anticipated that at the very least the panel will consist of one hematologist expert in leukemia morphology from both the USA and Ukraine, one hematopathologist expert in leukemia/lymphoma from both the USA and Ukraine, and one hematologist and/or hematopathologist from France.

Further development of the review protocol and organization of the review process itself will be the responsibility of Professor Burch together with Dr. Gudzenko.

D. Further Meetings with Dr. Gudzenko (and Later with Drs. Beebe and Howe) May 22 - June 6, 1998

① Pilot Project in Dnipropetrovsk Oblast to Trace and Bleed Sub-Sample of Clean-Up Workers: At our earlier meeting in Dnipropetrovsk oblast it was determined that 40 clean-up workers had been identified randomly from the Chernobyl State Registry as both resident in Dnipropetrovsk oblast and having up to date identifying information (i.e. they have been in attendance for their annual medical examination). It was originally planned to pre-test the pilot phase 1 study procedures by inviting this group of individuals to the oblast polyclinic for dosimetry questionnaire administration with a subset of these individuals then being asked to have their blood drawn.

However, it is essential in the pilot phase 1 study to not only assess the viability of study procedures in cohort members who are compliant with the ongoing annual medical examinations system but also to assess these same procedures amongst clean-up workers who have not been examined and therefore may be considered as lost to follow-up.

SUGGESTION: It was suggested that in addition to the original group of clean-up workers identified as living in Dnipropetrovsk oblast and having up to date identifying information that another random sample of clean-up workers (approximately 50) be chosen amongst those clean-up workers who have not been in attendance for their annual examination for one or more years and that this sample should be stratified by years of not being in attendance at the annual medical examination (ie. years of lost to follow-up) so that the number in each of those years is proportional to the total numbers in those years.

② Tracing, Questionnaire Administration and Collection of Blood Samples in Pilot Project: Attempts should be made to trace as many as possible of those clean-up workers who have been identified as being lost to follow. Of those who are subsequently traced a random sample of ten should be invited to come to the oblast polyclinic for questionnaire administration and blood collection. If some of these individuals do not show up for examination after the invitation, the invitation could be sent to another group of traced individuals until a total of ten clean-up workers from the the lost to follow-up group have participated in the questionnaire administration and blood collection. All members of the randomly selected group of clean-up workers previously identified as being under current observation should be invited to attend the oblast polyclinic for questionnaire administration and blood collection with the target being having questionnaire and blood specimens for 30 of this group so that the total number of clean-up workers with questionnaire information and blood collection will number 40. However, since the taking of blood samples from individuals and subsequently only processing 10 of them may be regarded as unethical a random sample of blood collection could be taken from the 40 individuals who have supplied questionnaire administration.

It was agreed that Dr. Tatiana Chekmareva, who is managing the Dnipropetrovsk Oblast Registry, be responsible for the initiation of the pilot project in Dnipropetrovsk. It is essential that all procedures used for tracing the lost to follow group and invitations etc. to questionnaire administration and blood collection for both the subsequently traced lost to follow-up group and those currently under observation be clearly documented. The results of all follow-up procedures should be recorded as successful or failures and by year of loss to follow-up. Despite the fact that many of the denominators in the different categories of study procedures may be small, it will be possible to determine response rates for various procedures and therefore assess the extent to which work in the pilot phase I study can assess the possible success of the larger cohort study.

Examples of the kinds of letters that could be sent to clean-up workers to invite them to participate in the study, respond to the dosimetry questionnaire and give permission for blood collection were discussed with both Drs. Gudzenko and Chekmreva together with suggestions for alternate

procedures in order to attain as high a response rate as possible among both the lost to follow up group of clean-up workers and those clean-up workers presently attending medical examination.

SUGGESTION: It was suggested that Professor Burch and/or Dr. Howe travel to Dnipropetrovsk oblast in the fall of 1998 to assess the quality and extent of the work done in this vital phase of the study. Such a trip on Dr. Howe's part may in fact coincide with his tentatively planned trip to Kiev, Ukraine to give a one week practical seminar on probabilistic record linkage (see Section II.C.5. of Dr. Howe's trip report). Additionally, Professor Burch would be able to work at this time with Dr. Gudzenko on the acquisition and organization of the required clinical and biological material for the anticipated diagnostic review of retrospective cases diagnosed with leukemias, lymphomas and related disorders. (A detailed description of this aspect of the study is given in Section C.1. of this trip report.)

E. Active Follow-Up of the Cohort:

Fieldwork Procedures: As per my suggestions for improving fieldwork detailed in my trip report of February 10-12, 1998, the introductory letter to possible cohort members has been simplified, contains a statement to the effect that without the participation of the clean-up worker the study cannot be successful, asks the clean-up worker to inform project staff about any plans he has for moving etc. The fieldwork for the pilot study in Dnipropetrovsk will include my earlier suggestions of involving local health nurses to trace and ask for the participation of clean-up workers, the sending of thank you letters to individuals who choose to participate in the study, etc. I discussed some potential problems with the current version of the dosimetric questionnaire with Dr. Gudzenko and she promised that the epidemiology group will take these into consideration together with any changes that are deemed necessary after the pilot work is completed in Dnipropetrovsk oblast. I was informed that any possibility of administering the dosimetric questionniare at the clean-up worker's home is not acceptable practice in the Ukraine. However, I was reminded that the interviewer in the pilot phase of the study in Dnipropetrovsk oblast, Dr. Chekmareva was one of those interviewers initially trained at a workshop held in Kiev in 1997 where the then current questionnaire was pre-

tested on 15 clean-up workers attending polyclinics in Kiev. I reiterated to Dr. Chekmareva during my present trip of how important it is to ask all questions in the questionnaire as similarly as possible to all respondents.

F. Passive Follow-Up of the Cohort:

① Other Data Sources: My earlier suggestions of tracing lost to follow up clean-up workers through other data bases were reiterated in meetings with Drs. Beebe, Gudzenko and myself. In addition to the possibility of using death records amongst clean-up workers identified by local physicians at the oblast polyclinic level through manually searching such records the need to approach other sources of information was stressed. These include the Ministry of Internal Affairs (i.e. the passport office), the "benefits file" from the Ministry of Chernobyl Affairs, and an as yet unidentified source which presumably maintains a file of "lifetime events". Despite the fact that these possible sources of information cannot be tested during the pilot phase it is imperative that they be officially approached during the pilot phase at a senior level, i.e. through Dr. Romanyenko's office, to determine what information is available, the extent to which the information is computerized and if it is possible for our study to access this information.

② Record Linkage: Details of the implementation of record linkage between the existing files with information on the clean-up workers is detailed by Dr. Howe in his trip report (See Section II,C. Points 1 to 5).

G. Overall Summary:

The three most essential requirements for the study investigators to concentrate on at this time are the determination of the feasibility of establishing and tracing the cohorts, the ability to establish reasonably accurate dose estimates for members of the cohorts and the determination of the existence of, and practical review of, essential clinical and biological material on clean-up workers diagnosed with leukemias, lymphomas and related disorders. With regard to the first requirement which is more particularly in my field of expertise I was somewhat disappointed in the seeming lack of any

practical fieldwork procedures having been initiated in the pilot phase I study in Dnipropetrovsk oblast. Therefore, one of the top priorities from my perspective is the immediate initiation and careful documentation of follow-up and pilot testing of study procedures in this oblast. In this respect I was impressed with the capabilities and demeanor of Dr. Chekmareva, who is responsible for this task in Dnipropetrovsk oblast over the next couple of months. Finally, with regard to the third requirement to establish the existence of appropriate clinical and biological material for successful diagnostic review in Ukraine I have established an excellent working and personal relationship with Dr. Gudzenko and am confident that she and I will be able to work towards confirming the availability of the relevant material for diagnostic review together with organizing and directing the work of a diagnostic review panel.

TRIP REPORT

GEOFFREY R. HOWE, PH.D.

VISIT TO KIEV, UKRAINE

Thursday, May 28, 1998
to
Friday, June 5, 1998

I. Introduction:

The first part of the visit, i.e., Thursday and Friday, May 28 and 29, was devoted to the leukemia project. In particular, extensive discussions were held with Dr. Natalia Gudzenko and her colleagues to discuss epidemiologic aspects of the study. In addition, discussions were held with Dr. Vadim Chumak and his colleagues, again, in consultation with Dr. Gudzenko to discuss dosimetric aspects, in particular, those which overlap with epidemiologic activities. A visit was also paid to the Chernobyl State Registry (Dr. Cortushin) to discuss some issues relating to the Registry.

The second week, i.e., Tuesday, June 2 to Friday, June 5, 1998, was devoted to the thyroid project.

II. Leukemia Project:

During the first two days of the visit, various topics were discussed at various times with different individuals. Therefore, this report is organized by topic rather than necessarily by chronology. The main topics discussed, and relevant comments and conclusions, follow.

A. Status of the Pilot Project in Dnepropetrovsk Oblast:

Both Dr. Gudzenko and Professor Burch had participated during the previous week in the field trip to Dnepropetrovsk to assess the current status of the pilot project. From discussions with them, the following points emerged.

① To date, little field work appears to have been carried out in Dnepropetrovsk, although plans have been developed for such field work and it is anticipated that such field work will start in the immediate future.

② A total of approximately 18,000 liquidators currently resident in Dnepropetrovsk oblast has been identified from the oblast or state Chernobyl registries. Liquidators in the oblast are still being added to the oblast Chernobyl Registry, including some who worked between 1986 and 1990. Last year in total there were an additional 500 liquidators registered. These, presumably, are individuals moving into the oblast from elsewhere, but it is unclear whether this is the only source of new registrants. Data on new registrants are sent from the oblast Chernobyl Registry (which is computerized) to the State Registry and are being added to the latter, although, presumably, they may already be on the State Registry if they were registered in another oblast previously. Presumably, there is a mechanism for avoiding duplication of such individuals in the State Registry but, again, the process of determining the existence of such duplicates is unclear.

③ Of the 18,000 liquidators on the State Registry currently resident in Dnepropetrovsk oblast, the great majority first worked at Chernobyl between 1986 and 1990; Dr. Gudzenko estimates that only a "few hundred" would not have worked during this period.

④ During the past year, approximately 14,000 of the 18,000 liquidators have been examined in one of the raion polyclinics. Of the 4,000 "lost to follow-up," approximately 2,000 have been seen within the past two years, 600 were lost three years ago, 300, four years ago, and 600 five or more years ago. It is anticipated that many of the 2,000 seen two years ago, but not in the past year, will reappear for a subsequent medical examination according to Dr. Gudzenko. If this is true, and the final lost to follow-up for that group is, in fact, similar to other years, i.e., about 600, then the medical examination system would be able to trace approximately between 80% and 85% of the cohort, which given that medical screening started more than 10 years ago, is encouraging. However, it appears as though the attrition rate is remaining relatively constant from year to year so

in a number of years in the future the lost to follow-up rate could become quite substantial and, thus, it will be essential that other follow-up mechanisms be available (see below).

⑤ Currently, 50 liquidators lost to follow-up three or more years ago have been identified in the State Registry and it has been confirmed at the oblast level that, indeed, these individuals are lost to follow-up, i.e., the oblast polyclinic has had no contact with them during the past three years. I recommended that the sample should be expanded to include those lost for one or two years since, of course, there is no guarantee that these individuals will return subsequently for medical examinations. I also recommended that the sample should be stratified by years of loss to follow-up and that the number in the sample in each of those years would then be proportional to the total numbers in those years. If possible, the sample size should be expanded to about 100 individuals, but if this is not possible, the sample should be expanded from 50 to the number that resources will permit.

⑥ I strongly recommended that the procedures to be used for tracing the sample of lost to follow-up liquidators should be clearly documented, and the order of priority of the various approaches to be used should be specifically delineated. In addition, of course, the result of the follow-up efforts should be recorded by the success or failure of the various procedures, and by year lost to follow-up.

⑦ One point which was not clear to me was what procedure would be employed with individuals who have been lost to follow-up but were traced during the pilot study. Ideally, at least some of these individuals should be invited to the polyclinic in order to undergo administration of the questionnaire and, ideally, a further subset would have blood drawn. At the moment, the plan appears to be to invite 40 individuals who are ***not*** lost to follow-up back to the polyclinic for questionnaire administration, with a subset of these individuals having their blood drawn. However, this latter group is likely to be more compliant than those lost to follow-up so it will be important to assess the participation rate by those lost to follow-up as well as those currently under observation.

⑧ In order to address the above point, I suggested the following sampling scheme. The first 50 liquidators should be randomly chosen from amongst those lost to follow-up. Attempts should be made to trace these individuals, and of those who are traced, a random sample of ten should be invited to come to the polyclinic for questionnaire administration and blood samples. If some of these do not turn up, the invitation could be extended to another group of traced individuals until the number is made up to ten. This would enable the administration of the questionnaire to ten individuals to be tested. A sample of 30 individuals from those ***not*** lost to follow-up should also be selected from the Chernobyl Registry and, again, invited to attend the polyclinic for interviewing and blood collection. Again, if some of these fail to turn up, substitutes should be invited until a total of 30 individuals have been interviewed. Thus, in total, 40 individuals will have received the questionnaire and blood will have been taken from all of them. However, it may be regarded as unethical to take blood from 40 individuals, but only use blood from ten individuals for further processing. If so, then the individuals whose blood will be taken will have to be randomly sampled from amongst the 40 individuals who received the questionnaire. This should provide a handle on response rates from amongst both those lost to follow-up and those not lost to follow-up, though denominators will be small and acceptance rates will be unstable statistically speaking.

B. Status of Oblasts Other than Dnepropetrovsk:

① It is planned to run tabulations for each of the other five oblasts in the State Chernobyl Registry which will do a head count of liquidators by years of loss to follow-up, i.e., not returned for medical examination, in the same way that has already been done for Dnepropetrovsk oblast. The software for this, of course, should already exist, but it seems unlikely that Dr. Cortushin and his staff would be willing to do this until the hardware from NCI is installed, which may well be a period of six months from now (see below).

② Dr. Gudzenko's "impressions" of the other five oblasts in relation to the likely quality of data in the State Registry from those oblasts are as follows:

- Donetsk and Kharkiv should be as good as Dnepropetrovsk;

- Sumskaya, nothing known;
- Kiev City appears to have problems in their database, but these problems are unknown to Dr. Gudzenko;
- Kiev oblast had problems two years ago in the sense that they sent identical data to that which had been sent the previous year; however, last year the problem appeared to have been rectified and updated data sent to the State Registry.

C. Passive Follow-up and Record Linkage:

① In addition to the active follow-up methods discussed above, I also stressed with Dr. Gudzenko issues of passive follow-up using record linkage techniques. At the moment deaths amongst liquidators are (sometimes) identified by a local physician in the polyclinic, notified to the oblast and eventually included in the Chernobyl State Registry. It is not clear how complete notification of deaths is by this method. Dr. Gudzenko said that currently death records for the oblasts are available on paper but not in computerized form. It might be feasible to conduct a manual record linkage amongst those lost to follow-up. For example, in Dnepropetrovsk if this was 15% of 18,000, i.e., 2,700 this ***might*** be feasible given the necessary resources. Exercises of this size, i.e., manual linkage have been carried out successfully in Statistics Canada using microfiche records; alternatively, it might be possible to do this on a sample basis to estimate how complete is the current system for notifying deaths.

② Some potential resources for passive follow-up other than the death records mentioned above were identified. These include the passport office (Ministry of Internal Affairs), but recently there have been some changes in passport numbers and it is unknown whether or not records of such changes have been kept and if they are computerized. Another possible resource is a "benefits file" of liquidators which, apparently, is kept in computerized form at the Ministry of Chernobyl Affairs, and, presumably, would have current addresses and possibly death information for liquidators. Another possible source is a file of "lifetime events" which, apparently, is maintained for Ukrainian citizens and contains records of births, marriages and deaths in computerized form and, apparently,

is kept by some ministry (unidentified). I strongly recommended that these various sources be investigated as soon as possible, in particular, the availability of computerized data, the content of such data records and the completeness of coverage of such files. In addition, I also recommended that, should these sources appear useful, permission to obtain access to them should be initiated as soon as possible but, clearly, this will probably have to be done at a senior level, i.e., Dr. Romanyenko's office. Investigation of the resources and obtaining of permission, where appropriate, should be carried out during the pilot phase of the study, though clearly these mechanisms cannot realistically be tested during the pilot phase.

③ As discussed above, eventually it may prove necessary to link the cohort file to passport records, the benefits file records and the "life events" records. This should only be necessary for those lost to follow-up through the medical examination system. It is hoped that these linkages can be carried out using computerized techniques if the appropriate records are indeed computerized. These linkages will almost certainly have to be carried out in the offices where the various files are held, i.e., the cohort records and record linkage system will have to be transferred from the Institute of Radiation Medicine to the relevant computer systems.

④ The other critical linkage will, of course, be that to leukemia/lymphoma records, both retrospectively and prospectively. Although, originally the plan was to make use of the cancer registry data for years when this was available, according to Dr. Gudzenko, this may not be feasible. The problem appears to be that the Institute of Radiation Medicine will not release the file of the cohort to the Cancer Registry and the Cancer Registry will not release their file of cancer incidence data to the Institute. There appears to be some rivalry between these two organizations, both of which regard themselves as research institutes and there appears to be a perception on both sides that the other side could use the data they receive in some unauthorized fashion. How real this is, and whether it can be resolved through future discussions, remains unclear. However, at the moment, it seems best to allow for the possibility that the linkages to the leukemia/lymphoma data will have

to be based on the extraction of the latter records from the oblast hematological departments and dispensaries.

⑤ In terms of implementing computerized record linkage procedures in the leukemia study, I propose that it would be much more efficient to provide training in Kiev in both the theory and practical application of such record linkage. This would take the form of a small group training session to be conducted by myself and a Russian-speaking programmer from North America who is familiar with the operation of a standard record linkage software package such as the generalized record linkage system maintained by Statistics Canada or a version currently in use at the Ontario Cancer Registry. The latter software is self contained and really runs in a PC environment. It can be purchased for a relatively modest amount of money which will be far less than the cost of developing a system from scratch in Ukraine. To date, there appears to be no experience or expertise in such record linkage in Ukraine. For example, the "linkages" conducted by Dr. Cortushin's staff for the thyroid project simply involved multiple passes of two files against each other and picking off "matches" on the basis of satisfying some arbitrary set of criteria. One pass is made for each set of criteria, all these potential matches are then given back to the endocrinology institute and how they are resolved is left to the discretion of the data processing people in the endocrinology institute who, again, have no experience in this area.

The small group training session could be held at Dr. Cortushin's institute in the fall, with participation by data processing personnel from the Institute of Radiation Medicine, the endocrinology institute, Dr. Cortushin's staff and data processing individuals from the Institute of Oncology, and any other organization which might be relevant. Thus, this would provide the ability to conduct such linkages in several institutions which may well be necessary for both the leukemia and thyroid projects. For example, it may be necessary to transfer the software expertise to conduct linkages against passport files, etc., as discussed above. This proposal would be developed more fully in the near future and submitted to NCI for their consideration.

D. Extraction of Information on Retrospective Cases of Leukemia and Lymphomas:

① It is planned during the pilot study to carry out the extraction of a sample of such cases from Dnepropetrovsk oblast. Apparently, the computerized cancer registration system has not yet started in this oblast, though it has started in several of the other oblasts which will be included in the full study, with data being extracted starting in various years. However, as indicated above, it is unclear that data from the Cancer Registry will be available for linkage purposes for the leukemia study.

② Dr. Gudzenko plans to visit the oncological dispensaries and hematologic departments of the remaining five oblasts during the pilot study to assess the state of records on historical leukemia/lymphoma cases. This probably should be done in conjunction with the obtaining of a sample of such cases for the pathology review (see below).

③ Dr. Gudzenko estimates that approximately 100 records of leukemia/lymphoma cases will be notified in Dnepropetrovsk oblast each year since 1987.

E. State Chernobyl Registry:

During the visit to Dr. Cortushin at the Chernobyl State Registry, the following points emerged:

① The computer equipment from NCI is unlikely to be installed and functional for at least 4-6 months. It seems apparent that no work on the leukemia project will be done by Dr. Cortushin and his staff until this equipment is installed.

② There seems to be no further progress in identifying and clarifying the various sources of data input into the register, other than that which comes directly from the individual oblast registries. It may, therefore, be unrealistic to expect that the representative nature of the registry in terms of all liquidators will ever be known with certainty. However, unless the registry was biased with respect both to dose and loss to follow-up, this should not affect the internal validity of the leukemia study which, of course, is the primary concern.

③ Apparently, files from both the military and the Ministry of Internal Affairs are currently physically at the Institute, but have not yet been integrated into the registry. However, it seems that no identifiers (e.g., names) are included in the military or Ministry of Internal Affairs files and, hence, such individuals cannot be included meaningfully in the study due to the inability to follow them directly by the means to be employed for those currently in the Chernobyl State Registry. It is also unclear when resources will be available to merge the three files together. My distinct impression from Dr. Cortushin was that this was on the "back burner," and it is not clear when or, frankly if, this will be achieved.

However, according to Dr. Vadim Chumak, there were three groups of military who participated in the cleanup. Only the "regular officers" are in the military file and not in the Chernobyl State Registry, with the two largest groups, namely, ordinary soldiers and reserve officers being contained in the State Registry. Dr. Chumak also thinks that these two latter groups are those primarily with any substantial doses. Hence, the loss of the military file may not lead to any serious loss of information. These facts should be clarified, and the actual numbers involved in each of the three groups identified, if possible.

④ We were told that passport numbers have not been included in the Chernobyl State Registry since 1992. It is not clear what this means, i.e., have all passport numbers been removed from the file or is it simply that no passport numbers have been collected from individuals registered since 1992? The latter would be relatively unimportant, but the former could be important.

⑤ As discussed above, it is clear that none of Dr. Cortushin's staff have any meaningful experience of record linkage. In particular, the concepts of probabilistic linkage, which I believe to be essential for the success of the leukemia study, are clearly foreign to them.

⑥ The Registry is currently in Foxpro Database format. Irena Gubina will be in charge of data processing at the Institute of Radiation Medicine's epidemiology group. She plans to maintain the

study cohort file in Foxpro, although she is also considering the possibility of using the ACCESS database system.

⑦ I promised to send Dr. Cortushin and his group material on probabilistic record linkage including the availability of software packages to conduct such linkages.

F. Leukemia Study Database Format:

① Discussions were held with Irena Gubina and Dr. Gudzenko about the possible database structure for the study. I suggested that it would be sensible to maintain two files, one on the full cohort and the other of the sub-cohort/cases. The latter file will, of course, contain substantially more information than the former. The database system to be used (Foxpro or ACCESS) should be chosen on the basis of convenience of usage and familiarity with those using the system in a hands-on fashion. However, one requirement which should be available in both databases is the ability to dump part or all of any records in a fixed length "flat file" in ASCII, since this will be the simplest way of interacting with other software packages, e.g., record linkage packages or statistical analysis software. This should not be a problem but will be very necessary since it will provide by far the easiest exchange of data between the database and such packages. For example, both the GRLS record linkage package and EPICURE which currently is the most appropriate package for fitting regression models to Poisson or Cox proportional hazards data require such flat files for data input. Further, for these purposes, records need only to be sequential and do not need to be accessed randomly.

② Dr. Gudzenko, in the second quarterly report, has laid out the information intended to go in the database. Although we did not review this in detail, I had two specific suggestions questions. First, the passport numbers do not appear to be in the record structure, and Dr. Gudzenko agreed to add this to the record structure. Secondly, it is not clear whether items such as residence which, of course, will change from time to time for some cohort members, can be recorded in multiple records in the file, i.e., is a separate record of each residence or, alternatively, is only the current residence

kept in the file? This is very important since one of the criteria for eligibility should be residence at the time of first employment at Chernobyl, and it still is not clear to me that this is actually available on the State Registry file.

G. Protocol for Pathology Review During Pilot Study:

I reviewed the draft protocol for the pathology review prepared by Professor Burch and Dr. Gudzenko prior to my arrival. In general, this appeared to be appropriate, although I did make a few suggestions for changes, as follows:

① The random sampling procedure needs to be more clearly delineated. In particular, a random sample stratified by oblast and year of diagnosis in addition to diagnosis needs to be obtained. However, it will not be possible to stratify simultaneously on all three variables given the relatively small number of individuals to be selected and possibly stratification by year may have to be dropped. In this case the randomization process should be based on a list for each oblast in which each entry on the list has a random year of diagnosis and a random page number. This will be used to access the apparently sequential logs of cases kept by each oblast, oncological dispensary or hematologic department. Thus, for example, to obtain a case of AML, one takes the first item on the list, goes to the log for that year and the page number for that year, then starts half way down the page and moves forward sequentially until identifying the first case with the final diagnosis of AML which then satisfies the other requirements, i.e., male and of an appropriate birth year.

② Cases should be restricted to those aged between 20 and 40, between 1986 and 1990 so that age at diagnosis distribution should be comparable to that for the liquidators.

③ The actual process for the pathology review needs to be defined much more specifically in a protocol which should be developed in collaboration with the hematologists and pathologists involved. However, this process should include some measure of inter-observer variability, and possibly intra-observer variability (the latter being done by randomly including material from a

single case twice in the review with the reviewer being ignorant of and blinded to this fact. Professor Burch conducted a similar exercise, i.e., a pathology review of brain tumors from a number of different countries at the IARC in Lyon last year and his experience in this case should be invaluable.

④ I pointed out that the primary function of the review was a) to determine the availability of material and b) to give the review team some experience working together. The process will not, of course, be able to identify false negatives, i.e., any diagnoses missed by the original oblast procedure, except to the extent that, for example, leukemia cases received a related diagnosis which had been extracted for the purposes of the pathology review. False positives can, of course, be identified during the review process. Comparison of the review diagnosis with the original oblast diagnosis will only be important if there are, indeed, cases for which the bulk of diagnostic material is unavailable, in which case we will have to rely on the original diagnosis to confirm a retrospective case. However, the general opinion seems to be that such material should be available even for cases diagnosed as long ago as 1987.

⑤ I suggested that the time of the pathology review should be set reasonably far in the future, since in my experience collecting clinical pathological material always takes longer than expected. Further, the clinical records will need to be translated at a minimum into English for the U.S. pathologists and, possibly, also into French for the French pathologists.

⑥ Since Dr. Matsushima, the original Columbia-based leukemia pathologist has now resigned, I suggest that I consult with Dr. Finch to identify a suitable individual to fill the second slot on the U.S. side for the pathology review, preferably with an individual from the Columbia system; this will also be discussed with Dr. Shelanski, Chairman of the Department of Pathology at Columbia.

H. Dosimetry:

Discussions were held with Drs. Vadim Chumak and Gudzenko concerning the current status of dosimetry. The following points emerged:

① Dr. Chumak states that there are five approaches to estimating dose:

- Analytic Dose Reconstruction (ADR): This is a detailed reconstruction based on knowledge of radiation fields and exact time and location information from the individual liquidator. This is ***not*** a process which can be carried out based on the current IARC-designed questionnaire and, in Dr. Chumak's opinion, can only sensibly be carried out for staff of the Chernobyl nuclear power plant since these would be the only liquidators familiar enough with the local geography to give appropriate information.
- Fuzzy set doses (FSD): This is a very approximate method which gives an average dose to individuals based primarily on their occupation and time spent in the 30km zone. Again, in Dr. Chumak's opinion, this is ***all*** that can be done from the current IARC questionnaire, and he also emphasized that the methodology itself required substantially further work for which currently no funding is available.
- Electron Paramagnetic Resonance (EPR): This, of course, is only available for those with tooth samples and Dr. Chumak emphasized that, again, funds are not available to maintain the system for tooth collection amongst liquidators which he has initiated. He also clearly regards EPR as the "gold standard" as far as such exists.
- FISH: This appears to be the only dosimetric method that could be available for the entire subcohort and all prospective cases to the extent that resources and response rates permit. However, Dr. Chumak stated that for cases, even pre-treatment bloods may be inadequate to obtain decent samples for FISH.
- Official Doses: These, of course, are the current doses contained in the State Registry, but in Dr. Chumak's opinion, these will only be available for a minority of such subjects.

② Dr. Chumak suggested that there should be an immediate investigation as to the possibility of obtaining post-mortem teeth from all cases.

③ There seems to me a major potential problem in dosimetry in that there appears to be unlikely any consistent method of dose estimation for all the relevant study members, with the possible exception of FISH, which, according to Dr. Chumak, may have problems for dose estimation in cases even if pre-treatment bloods are obtained. An issue which I think needs addressing immediately is the availability of methods for utilizing data collected from a number of sources with varying measurement error structures and which could contain both systematic and random errors. For example, if a high proportion of cases have EPR but only a small fraction of the subcohort have EPR can methods be developed to obtain unbiased risk estimates? I suggest that I raise this question with Dr. Heitjan, and possibly some of his colleagues from the Biostatistics Department. Intuitively, it would seem that if one knew the error structure for the various approaches, one could overcome bias by appropriate analytic techniques, but this remains to be determined.

④ I told Dr. Chumak that, in my opinion, it was essential that all individual dose estimates by all procedures be included in the epidemiology database since one would need this information to conduct appropriate risk analyses and uncertainty analyses. Apparently, he had wanted initially only to give a composite "best estimate" of dose for each individual, but I believe I persuaded him that all estimates were necessary.

I. Overall Conclusions:

I believe that substantial progress has been made during the pilot study, and I find this encouraging.

I plan to extract from my above comments certain specific questions to which the answers are currently not available and give these in summary form to Dr. Gudzenko so that she can either ask these questions or obtain the relevant information. The top priority items, in my opinion, are to initiate the fieldwork in Dnepropetrovsk oblast, which should be done as soon as possible, and to

pursue the question of the appropriate method of using different dose estimates from different sources for different members of the subcohort and cases in order to obtain unbiased risk estimates. As stated, I plan to initiate this process on my return to Columbia as soon as possible.

May 25, 1998 to June 6, 1998

II. STUDY OF THYROID CANCER AND OTHER THYROID DISEASES IN UKRAINE FOLLOWING THE CHERNOBYL ACCIDENT

A. May 25, 1998 Meeting with Dr. A. Derevyanko, Head of Epidemiology Group and Dr. V. Tereschenko, Vice-Director of Institute of Endocrinology and Metabolism, Deputy Director of Project.

① Prior to the plenary session of the study which met on June 3, 1998 I met with Drs. Derevyanko and Tereschenko and reviewed progress to date particularly with respect to fieldwork accomplished in the pilot raion of Ivankiv.

② Background: A 20,000 member cohort of children who were between the ages of zero and eighteen years in 1986 has been established chosen by dose category with approximately 10,000 in the high dose range, and 5000 each in the two lower ranges. (This list of children is referred to as the Likhtarev list). This cohort of children were resident in raions of the oblasts of Chernihiv, Kiev and Zhytomyr at the time of the accident.

③ Two mechanisms to date have been utilized to locate the current addresses of this cohort: manual searching of records at local medical institutions and linkage of the dose file (Likhtarev list) with the Ukrainian State Chernobyl Registry (Dr. Cortushin, Director, Ukrainian Center of Information Technology and Chernobyl State Registry). It is my understanding that these two methods have been done for a number of raions with varying success rates (some as low as 5 percent, others as high as almost 90 percent). Dr. Derevyanko has informed me however that for the raions other than Ivankiv the numbers for the manual searches have not as yet been entered into the computer and therefore it is not possible at the present time to determine which of the two mechanisms for updating current information on the cohort is the best.

④ Ivankiv Raion: For Ivankiv raion, which has been chosen by the investigators as a "pilot" raion, linkage between the Chernobyl State Registry and the Likhtarev List has found approximately 50 percent of the cohort members while manual searching of medical records in local institutions has found 40 percent. However, it is important to remember that these two categories do in fact overlap and are not mutually exclusive.

The progress to date in determining current addresses for children living in Ivankiv raion has not in fact changed since my first trip in February, 1998. There are current addresses (as far as it can be known) available for 494 (70 percent) of the total 737 potential cohort members who were between zero and eighteen years old at the time of the Chernobyl accident who are still resident in Ivankiv raoin). Therefore, current addresses are still unaccounted for 243 of the cohort (30 percent) in Ivankiv raion.

Results of Interviewing/Examination Fieldwork to Date - May 25, 1998:

Letters of invitation to potential participants in the study were sent in January of this year to the 494 individuals with known current addresses. In point of fact, these invitation letters were not sent by mail to these individuals but rather they were personnally delivered to them by local area medical staff. The letters explained the nature of the study to the potential cohort members and requested them to send back to study headquarters a postcard which had been attached to the letter indicating their response to the invitation.

As of May 25, 1998, 146 agreed to participate in the study, 4 absolutely refused and there was no response from 344.. Subsequently, the local medical staff re-approached the non-responders and asked them in person to participate in the study. Evidently, of these, approximately 80 percent indicated that they would participate in the study.

Mobile Team: Since my first visit to Kiev in February of 1998 one mobile team has been established and this team has travelled to Ivankiv raion in April and May to recruit and therefore interview and examine cohort members with the final result that 160 cohort members in Ivankiv raion have been recruited, interiewed and examined. It is my understanding that the mobile team is continuing its work in Ivankiv raion so these numbers should improve.

SUGGESTION: As per my concern expressed in my first trip report, that too much leeway has been given to the Ivankiv local area medical staff in implementing the study in this raion it is apparent that there is little or no documentation to date of the on-going study procedures. Without such documentation it is impossible, for example, to determine which recruitment procedures work best and which methods should be dropped owing to poor response etc. It is absolutely essential that all study procedures used and success rates of the various approaches used by project staff to trace and recruit cohort members is carefully documented. It has been suggested by Dr. Derevyanko that obtaining accurate counts of various procedures used in Ivankiv raion to date may possibly never be available from medical staff.

⑤ Recruitment of Evacuees From Prypiat Living in Kiev: Drs. Derevyanko and Tereschenko explained that when the Likhtarev File was linked to the Chernobyl Registry a number of children who were evacuated from the Prypiat area were found to have current addresses in Kiev. A list of these children, numbering 542, was subsequently sent to the Computer Center of the Kiev City Department of Public Health and current addresses in Kiev were found for 413 potential cohort members.

As of the first week in May, 1998 the epidemiology group has been approaching these individuals by telephone, inviting them to be examined and interviewed at the Institute of Endocrinology and Metabolism. To date (May 25, 1998), 74 individuals have been recruited into the study and given the interview and examined. As this aspect of the study has just begun there has not as yet been any

tabulations of response rates. In this regard however I did stress to Drs. Derevyanko and Tereschenko the importance of documenting all procedures being used for tracing and recruiting cohort members by telephone in this group of individuals.

⑥ Related Activities Since February 1998 Trip:

a. Updating of Identifying Information on Cohort Members Lost to Follow-Up: As mentioned above, in Ivankiv raion there is no current address information available for 243 of 737 potential cohort members ie. 30 percent of the cohort. In this regard, the Ukrainian Ministry of Health has requested government officials in the Ministry of Internal Affairs (passport office) for all known current addresses known in their files of children who are listed on the Institute of Radiation file (the Likhtarev file) in Ivankiv and all other raions in the study. This request was in fact made quite some time ago and I suggested that the request be followed up immediately.

b. I was encouraged to learn that attempts have been made by the Epidemiology Group to publicize the study. Dr. Tereschenko wrote a description of the Thyroid Study which was published on April 1, 1998 in a medical newspaper that most medical workers have available to them. In addition a somewhat briefer description of the study appeared in the April 10, 1998 edition of a local newspaper in Ivankiv raion.

B. Further Meetings With Drs. Beebe, Derevyanko, Mitchell and Howe, June 3 to June 6, 1998

As a result of our meetings I will comment and make suggestions on the following areas in the implementation of the study in Ukraine:

- the establishment and ascertainment of the cohort including follow-up;
- the in utero study;
- the general area of fieldwork including letters of invitation to potential cohort members, questionnaires, interviewer training, interview monitoring;
- the documentation of study procedures;
- coding and data entry;

① Establishment and Ascertainment of the Cohort Including Follow-Up: The Data Control Center indicated in the plenary session of June 3, 1998 that after linking the dose file (i.e. the Likhtarev file) with the Chernobyl State Registry that approximately 4800 of the 20,000 cohort was found ie. only 25 percent of the cohort. Additionally, as noted above specifically for the Ivankiv "pilot" raion, after utilizing both this mechanism and manual searches of local medical records, 30% of potential cohort members in this raion were unaccounted for.

In this regard Dr. Howe has suggested that it would be possible to introduce a probabilistic record linkage system into the Chernobyl State Registry that might reduce any problems arising from the previously conducted matching between the Likhtarev file and the Chernobyl State Registry file. He would conduct a training workshop in Kiev at the registry utilizing practical ready made software to conduct linkages and he hopes that this mechanism might determine whether there is any data missing in the Chernobyl Registry for individuals from the Likhtarev file.

SUGGESTION: I would suggest that in addition to the initiation of new improved linkages between the Likhtarev file and the Chernoyl State Registry file that as soon as possible linkages be made to other existing database files in Ukraine. In this regard the Ministry of Health's request to the Ministry of Internal Affairs (passport offices) to help in determining current addresses the passport, offices may have for individuals on the dose file should be followed-up immediately.

SUGGESTION: With regard to follow-up of cohort members who attend screening and are administered the dosimetry and medical history questionnaires it is essential that at the time of screening and questionnaire administration cohort members be asked to give identifying information such as addresses and telephone numbers for their parents, other relatives or potential contact persons such as older friends as well as some kind of indication of any plans they may have for re-locating. The initiation of these procedures immediately is necessary if future contact with the cohort members is to be successful.

SUGGESTION: In order to facilitate continued follow-up of cohort members who are currently being entered into the study it is essential (as I mentioned in my first trip report) that thank you letters be sent to individuals following their attendance at screening and interviewing. It is my understanding that, owing to lack of computer facilities at the present time, this has in fact not been done for those recruited to date.

② In utero study: The planned in utero study was discussed briefly. To date, evidently little has been undertaken in this study except for linking a list kept by the Institute of Pediatrics with the dose measurement file. The "matching" rate was reported to be only 16%.

SUGGESTION: As suggested in both the study of leukemia amongst cleanup workers in Ukraine and thyroid cancer in children in Belarus, Dr. Howe would conduct a training workshop in Kiev on probabilistic record linkage. The use of this system may well improve linkage between the pediatric and dose measurement files.

③ Fieldwork:

Invitation Letter: I was encouraged to learn that as a consequence of my first trip to Kiev in February of this year that the letter of invitation to potential cohort members was to some extent modified to make it more "user friendly" by simplifying medical terminology, inviting the potential respondents to telephone the study center with any questions they may have etc.

SUGGESTION: However, as a consequence of familiarizing myself with the work of the mobile team and other on-going fieldwork procedures since that first trip, other changes to the invitation letter are necessary as well as determing when it should be sent to potential respondents:

- In order to facilitate the collection of fasting blood samples the invitation letter should be sent out to potential cohort members further in advance and should include a statement that a fasting type of blood collection will be requested;

- The mobile team indicated that for children who were less than 10 years of age at the time of the Chernobyl accident questionnaire information on a number of factors such as history of illnesses in relatives and dose information around the time of the accident was inadequate. I would suggest therefore that the invitation letter to potential cohort members include a statement to the effect that the parents of the child come to the examination with the child if possible, that if this can be done that the parent (or other relative, guardian etc) be that person who knows the most about the child at the time of the accident, and most importantly, that the subject areas covered by the questionnaire be indicated in the invitation letter so that the child and his/her parents can be better prepared to answer questions.

Questionnaire and Interview:

SUGGESTION: After familiarizing myself with the experience to date of the mobile team and the team at the Institute of Endocrinology and Metabolism it is necessary to change the questionnaire in the following ways. First of all, since different questions may be answered by different people depending upon the information sought by the questions it is essential that the questionnaire indicate who or what combination of people answered the questions. It may be too cumbersome to do this on a question by question basis but it could be done by having the interviewer indicate at the end of the questionnaire who gave all the information, who gave the most, whether it was equally answered by, for example, the child and his/her parents etc. Such a description of the interview process could be further specified by indicating who gave most of the anwers etc. to which kinds of questions ie. history of residence, questions on milk consumption etc.

Additionally, it would be a good idea to include at the end of the questionnaire a semi-quantitative assessment of the " reliability" of the information given by the respondent(s). The interviewer could, for example, estimate this "reliability" by indicating on a five point

scale (ranging from very reliable to very unreliable) where the respondent(s)'s answers fit. This estimation could also be done (as above) by types of questions asked. Although this kind of estimation by interviewers is quite subjective it nevertheless can be useful in identifying and therefore eliminating from analysis those questionnaires which appear to be unsatisfactory.

SUGGESTION: The mobile team indicated that cohort members who were over the age of 10 -12 years at the time of the Chernobyl accident responded fairly well to the questionnaire. Therefore, it is essential that a cut-off age below which only questionnaires completed by the knowledgeable parent or other person at the time of the Chernobyl accident be included in the study.

SUGGESTION: It is essential in the interview situation where the cohort member attends but is unable to answer the questions that the procedures followed in having that individual have his/her parents or other knowledgeable person fill out the answers subsequent to attendance at screening be clearly documented and described. Such monitoring of questionniare completion will of course be aided by the inclusion of questions determining who answered what questions as detailed above.

SUGGESTION: Possible procedures that could be initiated to train the interviewers and monitor the interviewing of cohort members were discussed with Dr. Derevyanko including the use of videos (which I am currently assessing at Columbia University), the attendance at interviews by investigators to ensure that compliance with standard interviewing techniques are being followed by all interviewers, re-interviewing of a sub-sample of previously interviewed cohort members , and regular meetings of all interviewers to discuss any problems.

④ Documentation of All Study Procedures:

SUGGESTION: At the moment, especially with respect to the fieldwork being done by the local medical staff in Ivankiv raion, there is little or no documentation of the procedures being used to trace and recruit potential cohort members and success rates for these various procedures. In meetings with Drs. Beebe, Derevyanko and Howe it was suggested that for each potential cohort member a "case location" form be generated by the computer which would enable the investigators to track the progress (or lack of) of each individual in the study (ie. giving details of how the potential cohort member was located, the number and kind of appproaches used to recruit the cohort member, the responses to these different approaches, and the success of these procedures to locate and recruit these individuals).

⑤ Coding and Data Entry: It appears that at the present, none of the information entered on the forms for those recruited and examined to date has been entered into the computer.

SUGGESTION: It is absolutely necessary that coding and data entry be initiated as soon as possible. The reasons for this are twofold. First, if this component of the study is not begun soon, in my experience, studies have a way of "running away from you" and the investigators are swamped with unintelligible data. Second, and more importantly, it is difficult to assess quality control of the data. With respect to coding, it is imperative that a coding manual be compiled and that coding staff be assigned and trained utilizing this manual.

The process of coding forms for data entry can be further facilitated by having as many as possible forms pre-coded. For example, where forms ask for a simple dichotomized answer, e.g., gender, predetermined numerical codes can be assigned on the forms themselves; example: male = 1, female = 2.

SUGGESTION: I have asked Dr. Buglova, Head of the Epidemiology Group in Belarus, to send to Dr. Derevyanko, copies of all the forms used in the Belarussian study, as examples, since many of the BelAm forms have, in fact, been pre-coded.

C. **Overall Summary:**

I have established an excellent rapport with Dr. Derevyanko and because of this, I am optimistic about our future work together. One of the most essential areas for the study investigators to concentrate on at this time, amongst others, is the documentation of all study procedures (both in the past, if possible, and the future) together with coding and data entry.

III. Ukranian Thyroid Study:

This was my first visit for a number of years to the Institute of Endocrinology in Kiev in connection with the study of thyroid cancer. Overall, my impression was that a good start had been made to the study and, although a number of issues were identified during my visit which require attention, the study appears to have been initiated satisfactorily and has the potential for yielding meaningful epidemiologic data on the relationship between thyroid disease and exposure, primarily to 131_I.

The areas on which I focused and on which I provide my detailed comments below, were: a) the definition, location and recruitment of the cohort.; b) issues relating to the various questionnaires; c) coding and data entry; and d) the possibility of a preliminary statistical analysis based on a small number of thyroid cancer cases. My detailed comments follow.

A. Definition, Location and Recruitment of the Cohort:

① In terms of defining the basic cohort to be included in the study, there are two fundamental requirements. First, the selection process should be such so as not to introduce any meaningful biases in the risk estimates and, secondly, the cohort should be of adequate size, i.e., with an expectation of a sufficient number of cases to yield adequate power to provide risk estimates with sufficiently narrow confidence intervals to address questions such as the relative biological efficiency of ^{131}I and external gamma radiation in inducing thyroid cancer.

With respect to bias, certain principles need to be borne in mind. These principles are, of course, well established in the epidemiologic literature, but do have immediate and important practical consequences for choosing the cohort. The most immediate practical consequence is that if, of the initially selected 20,000 cohort, only 50% can be traced and included in the study, this does not

necessarily affect the results of the study, and one may validly go on and locate a further 50% of the next 20,000 and so on until the required sample size is reached to provide the necessary power. Unless the sampling is biased with respect to the combination of dose and disease risk, failure to locate a substantial proportion of the initially selected cohort would have no impact upon the relative risk estimate although potentially a greater influence on excess risk estimates. The reality may be such that, indeed, one has to live with substantially lower location and response rates than would be ideal.

Virtually all cohort studies are never truly representative of the target population because, inevitably, there will be a substantial non-response rate; this is true, for example, of such well known cohort studies as the British doctors' study (response rate about 50%) and the nurses' cohort study (response rate about 20%). Yet the results of these two studies are universally accepted as valid. The issue of representativeness relates only to the so-called external validity of the study, i.e., can the results be applied to all individuals; in general, there is no reason to expect that results from internally valid studies will not be applicable to the general population, particularly when results are presented specifically for factors such as age at exposure and gender.

In summary, I would suggest that the most important thing is to build an adequate sized cohort and not worry too much about its representativeness; the efforts should be put into obtaining enough people and excessive effort should not be put into exhaustively trying to trace all members of the initially identified cohort.

② The present study presents an ideal opportunity to conduct either case-control or case-cohort within cohort studies. This is not analogous to the leukemia study where, in fact, the use of such designs was based upon cost considerations, where these study designs have the same potential biases as conventional case-control studies. In the present situation, i.e., the thyroid study, the case-control and case-cohort within a cohort study design would not be subject to the biases of conventional case-control studies, but would provide the same degree of bias as the full cohort study

but at a fraction of the cost. In particular, such a design would involve carrying out laboratory processing of blood samples and working up individual doses *only* for cases and a sample of the full cohort. For example, if laboratory workup and dosimetric workup were carried out for 5,000 instead of 20,000 individuals, costs for these activities would be reduced by about 75%, without any meaningful loss of efficiency. Questionnaires and blood samples would, of course, have to be stored so that they could be retrieved for cases as they occur, but I assume this will be done anyway. I realize that it might be hard to sell this concept politically, both in the U.S. and Ukraine, but it would lead to very substantial savings on the resources required; alternatively, the same resources could be spent but the size of the cohort could be substantially enlarged and, hence, the number of cases could be substantially increased and, hence, the efficiency could be substantially improved.

③ Currently two sources are being used to locate the cohort. "Record linkage" has been carried out between the dose file of Dr. Likhtarev and the Ukrainian State Chernobyl Registry. In fact, this is not a linkage in the true sense since it simply involves repeated passes of the two files against each other using a different series of criteria for exact matching without any consideration either of the relative frequency of the identifying items, nor rates of errors in recording data. The process by which the final "matches" were resolved at the Institute of Endocrinology is not documented, nor could it be described by the individuals from the DCC.

The results of this "linkage" are, to put it mildly, dubious. The table attached shows the percentage of cases on the dose file "matched" to individuals in the State Registry. Even though the great majority of the Likhtarev subjects are supposed to be on the Registry, the overall matching rate, i.e., 24% is extremely low. Further, it varies substantially from raion to raion varying from 4% to 51%. The problem could be in the matching process used, or could be in the data on the Registry, or a combination of the two.

I suggest that the first step would be to introduce, as soon as possible, probabilistic record linkage into the state registry and re-run the linkages in order to minimize any problems arising from the

previously conducted linkages. It should then be possible to determine whether there is, indeed, a problem in the State Registry in terms of missing data for individuals from the Likhtarev file.

The other method currently used for locating individuals is through the local raion medical records, these searches being conducted by the local medical staff. The numbers are also shown in the table (see attached).

As will be seen, this process has an overall tracing rate of 42%. The overlap of subjects traced by linkage and manual search is currently only available for Ivankoff raion, for which the total tracing rate is 67%. However, this cannot be extrapolated to the other raions since the linkage tracing rate is much higher in Ivankoff than in other raions.

What is currently lacking, however, which is very important, is adequate documentation of the procedures and success rates of the various approaches used by the local medical staff for tracing individuals. My suggestion would be that for each potential study subject a "case location" form be generated by the computer which would require details of how a particular case was located by the local medical staff, the number of contact visits that had to be made, the dates of such visits and the success of any different approaches used to locate and recruit individuals. These forms would be sent from Kiev to the local medical staff and would then be returned by the local medical staff to Kiev for entry into the computerized "administrative file" in the DCC. This would help establish the success rate of the various methods.

Assuming that the overlap rate between the two tracing methods is the same for the other raions as for Ivankoff then we can estimate, at this stage, the expected overall success rate based on the combination of the State Registry and local medical staff.

Thus, overall, one might expect a successful location rate of about 65% from these two methods. The question then becomes as to whether other methods of tracing, e.g., the passport office, should

be utilized to increase this rate, or should a further sample of the full potential cohort of 80,000 be selected and the two existing tracing methods continue to be used as the only methods. I think this would best be answered after the repetition of linkage using probabilistic linkage approaches at the State Registry, since, hopefully, this might improve the overall tracing rate. I think it worthwhile to pursue the possibility of using resources such as the passport file at this stage, but would hesitate to recommend their full-blown use until the linkage has been repeated.

In order to estimate the final size of the cohort, it is necessary, of course, to estimate not only the location rate of study subjects, but also their response to the invitation to screening. The only data which I have available at the moment are from the one mobile team whom we met with in Kiev, who stated that 53 of the 90 invited individuals had actually turned up, i.e., a participation rate of 59%. If this is multiplied by the approximate estimated location rate described above, we obtain an overall inclusion rate of 38% based on the approaches used so far. This would mean that approximately 11,600 of the 20,000 initially selected cohort would participate in the study. If we were to multiply this by four (given the size of the Likhtarev file of 80,000) we would, thus, recruit about 40,000 study subjects into the final cohort. It is probably worthwhile recalculating the power of the study based on this number or, preferably, based on the combination of this number with the data from Belarus, before decisions can be made as to using alternative methods of location or improved methods for study participation, e.g., giving gifts to those who participate.

④ During the visit to Kiev, various approaches to inviting study subjects to participate were considered. I would strongly recommend that only a single letter be sent to potential study subjects (i.e., the letter that is currently sent) coming from the Ministry of Public Health, outlining the study and that such a letter should be sent, ideally, several weeks prior to the visit by the local medical staff. I see absolutely no point in including the postcard for return since all this does is to identify the extremely small number of subjects who will send the postcard back saying that they do not wish to participate (4 out of 594 in the experience to date). Many people simply do not return the postcard, but still participate in the study. The letter would then be followed by the personal visit

of the local medical staff asking the individual to participate and scheduling a suitable date for the visit. I note, at the moment, the scheduling is done entirely by the local medical staff which is not ideal, but there seems to be little practical alternative, and so far it appears as though the system has worked, i.e., sufficient study subjects are recruited to keep the mobile teams busy, but not too many are recruited to flood the resources of the mobile teams.

⑤ The issue which has thus far appeared not to have received too much attention is the necessity for inviting people back for the second and subsequent screenings. I would suggest that information be obtained at the time of the first screening on names and addresses of subjects' parents, and other relatives or potential contact persons such as friends. It might also be useful to attempt, if possible, to get some information on any expected plans in two to three years time for the study subject, e.g., does he/she anticipate going away to some educational institute at this time, do they have such institutes in mind, etc. These procedures are fairly standard in cohort studies where you need repeated contact with study subjects, and obviously need to be initiated now, otherwise future contact is liable to be problematic.

B. Issues Relating to the Various Questionnaires:

① The current questionnaires need modifying in several ways. First, it will be important to identify the source of information, i.e., parents, child, or combination of the two. Although this can be done on a question-by-question basis, it seems more practical to allow the interviewer at the end of the interview to characterize the interview into, say, five categories, i.e., all responses provided by parents, most responses provided by parents, responses equally provided by parents and subject, most responses provided by subject, all responses provided by subject. This should be adequate for any statistical analysis. Secondly, there should be some semi-quantitative estimate of the "reliability" of the interview provided by the interviewer. Again, this could be a five-category scale, ranging from "seems very reliable" to "seems very unreliable." Although this inevitably is somewhat subjective, it has proved useful in other studies, particularly to eliminate what appear to be unsatisfactory interviews.

② There needs to be a specific policy as to the age at which information can be requested solely from the study subjects, e.g., from those who were age 10 or 12 or more at the time of the accident. Information on anyone under this age which is not obtained with the parents' cooperation probably should not be used.

③ Attention needs to be paid urgently to the issue of setting up appropriate coding boxes and codes on the questionnaire; it appears as though much of the coding could be done directly by interviewers, e.g., sex, etc. The boxes need to be set on the right hand side of the questionnaire for ease of data entry, and boxes which will be filled in by the interviewer as opposed to those by coding staff, should be distinguished from each other, e.g., by shading those boxes to be completed by coding staff.

④ Finally, there needs to be an ongoing assessment of the questionnaire, e.g., by routine meetings of interviewers to see whether certain specific problems are regularly emerging during interviews, so that if need be the questionnaire can be corrected.

C. Coding and Data Entry:

① This process needs to be initiated as soon as possible. Without coding and data entry quality assurance for the questionnaire data will be hard to tabulate and examine. In particular, a coding manual needs to be developed as soon as possible in collaboration with those who have already conducted interviews and who may well help to contribute appropriate suggestions for coding.

② Coding procedures need to be standardized, e.g., using the same codes for the same responses, e.g., 1 for "yes," 2 for "no," 9 for "don't know" (don't know should ***not*** be coded as a blank since one cannot distinguish this from simply a failure to code).

③ There should be two files of data for study subjects. The first is an "administrative file" on which ***all*** potential study participants are included. Currently this would include the 20,000 selected

from Likhtarev's file. The information to be contained in this file would include identifying data, study I.D., information from the case recruitment sheet, date of first screening, availability of information, of laboratory data, dosimetric data, detection of any thyroid pathology, etc. (the latter field could simply be scored yes/no). The file would also contain information on second and subsequent screenings, e.g., letter sent to invite for second screening and the date sent, date of second screening, etc. This administrative file will be the basis for tabulating response rates, keeping overall track of the study, generating letters of invitation, etc. The second file will be the study database containing the detailed information from the questionnaire, detailed laboratory results, detailed clinical data, etc. This of course would need to be set up in a standard database format since it will contain repeated segments of information from each screening visit. Arguably, the highest priority should be given to the establishment of the administrative file since it is likely to be easier, and the information will more urgently be needed.

④ Consideration needs to be given to the best method of interfacing the database for the study file to other software, e.g., SAS and other analytic software programs.

D. Preliminary Estimation of Risks:

It has been suggested that risk estimates could be derived from the study using only a small number of cases when available, e.g., 20-30. I recognize the desirability of obtaining initial estimates from the study as soon as possible in order to underpin its feasibility and utility. However, I am very concerned that such estimates and the manner in which it is currently proposed to obtain them could be misleading and substantially weaken the perceived credibility of the study.

My first concern is that any estimates will inevitably have very wide confidence intervals and could, for example, conceivably give rise to estimates of negative risk coefficients; if they are positive it is certainly possible that the confidence interval could include an rbe of 0.1or 10.0 compared to risks for external gamma radiation.

Secondly, the difficulty of fitting the data does not seem to be fully appreciated by Dr. Likhtarev's team who plan to carry out risk estimation. The model to be fitted would be the linear excess relative risk model fitted to proportional hazards data, and the only software that I am aware of currently available to fit such models is the PEANUTS module of the package EPICURE which produces likelihood based point estimates and interval estimates. However, the program, to the best of my knowledge, it is not currently available in Ukraine, and requires appreciation of the subtleties involved in fitting such models. Fitting other statistical models using approximate methods is likely to lead to very misleading estimates. A simple example is that if confidence intervals are based on the ratio of the point estimate to its standard error, which is often done, the resulting confidence intervals are completely erroneous.

The third, and perhaps the most worrying possibility, is that the selected cases and selected individuals with dose measurements could be a highly biased sample in some way which might not be recognized by the dosimetrists. This, of course, would result in meaningless risk estimates.

As I say, I understand the desirability of producing some risk estimates, and that Dr. Likhtarev's group feel that they should be the individuals to do it given their ownership of the dose data. However, I would argue most strongly that any exercise of this nature needs to be undertaken most cautiously and would need the involvement of an individual with substantial experience in conducting risk estimation in radiation cohort studies. I would be most happy to offer my own services to Dr. Likhtarev's group in this respect, and would expect no recognition of any contribution I might make so this would not detract in any way from credit going to him and his group. However, I realize it might be very difficult to get Dr. Likhtarev to accept this solution, but as I say, I think we have a major potential problem here.

State of the 20.000-cohort for 01.06.98

Raion		Found			%	
	Total	in Chern.Reg	Manual search	Total	in Chern.Reg	Manual search
Chornobyl	1484					
city Prypyat	1584					
Polisya	1399	511			36,53	
Ivankiv	737	378	297	494	50,61	40,30
Kiev oblast	**5204**	**884**	**297**		**16,99**	**5,71**
Kozelets	2089	215	1156		10,29	55,34
Repki	1377	572	793		41,54	57,59
Chernigov	2858	997	1386		34,88	48,50
city Chernigov	1179	51	1024		4,33	86,85
Chernihiv oblast	**7503**	**1835**	**4359**		**24,46**	**58,10**
Narodichi	4279	811	1256		18,95	29,35
Ovruch	3072	714	2157		23,24	70,21
Zhytomyr oblast	**7351**	**1525**	**3413**		**20,75**	**46,43**
city Kiev		**542**	**413**			
Total	**20058**	**4786**	**8482**		**23,86**	**42,29**

Date: Mon, 29 Jun 1998 07:31:09 EDT
From: EGslowski@aol.com
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Subject: kiev-ellen greenebaum

TRIP REPORT TO KIEV AND MINSK - JUNE 1998

Ellen Greenebaum, M.D., Senior Cytopathologist, New York Presbyterian Hospital, Associate Professor of Clinical Pathology, College of Physicians and Surgeons, Columbia University

This was my first trip to Kiev and Minsk as part of the Columbia-NCI Contract to study the long term effect of the Chernobyl disaster on the thyroid gland of exposed children. My comments will be confined to Cytology and Pathology, emphasizing cytology.

Kiev, Ukraine:

The Cytology Laboratory at the Institute of Endocrinology and Metabolism is referred to as the "Laboratory of Functional Diagnosis". The Laboratory head is Dr. Yu.M. Bozhok. There are four other cytologists: Dr. Anna Zelinskaya, Dr. Tonya Khorozhenko, Dr. Anna Uscimenko and Dr. Delina Kulinichenko. Institute of Endocrinology and Metabolism, Vyshgorodskaya Str. 69, Kiev - 254114, Ukraine, Phone (044) 431-02-96 or 431-04-22.

Cytologists' background

Ukranian cytologists' training consists of a five year University Program, after High School, resulting in a degree of Doctor in Biology. The five years of training include basic sciences, biology, anatomy, histology, and cytology. This amount of training is equivalent to that received by cytotechnologists in the United States: a four year college degree plus one year of training in cytology including anatomy and histology. No medical doctor or pathologist is involved in slide review or laboratory management.

Laboratory supervision

The senior cytologist and supervisor, Dr. Bozhok, has a wealth of experience in thyroid cytology and has compiled an atlas of typical diagnostic findings and their features; this atlas has been copyrighted and published by Germans involved in Chernobyl aid and distributed to other Ukranian Cytology Laboratories.

Exciting technical, cytodiagnostic, and prognostic scientific research is being carried out in Dr. Bozhok's laboratory, although not as a part of the Chernobyl cohort study.

Case volume

The number of patients with fine needle aspirations is between 1300 and 3000 cases per year; roughly 10 to 15 cases per day, 4 days per week. When multiple nodules are aspirated they are sublabelled A, B, C, D, etc, but not counted as separate cases. The lab receives roughly 6 to 10 slides per case. It is not clear whether inadequate slides were discarded or were saved and counted. The log book for a random day included 12 patients, 79 slides. A different two day period combined had 198 slides.

Although I did not have a chance to review any of the cytology cases from the Chernobyl Cohort project, I was shown a tabulation of the case numbers with the following results:

The number of FNA's of thyroid in 1997 was 1546 adults and 352 children, however, only two cohort patients have had fine needle aspirates since the study began. The number of aspirates performed in 1997 is higher than in prior years; in 1995 and 1996 combined, there were thyroid FNA's on 2129 adults and 344 children, hence the number of children per year had at least doubled in 1997. The numbers are predicted to continue to increase because of Chernobyl disaster effect, screening projects, increased number of

sonographers (1 in 1984, 2 in 1994, and 4 in 1998), improving sonographic equipment, detection and aspiration of smaller nodules. These factors will contribute to the increase in number of positive fine needle aspiration biopsy results, however it is not yet determined whether all of these tumors detected are of prognostic significance.

Cytology laboratory Workflow and equipment

The Cytology laboratory work distribution is set up so that one of the four cytology Doctors screens and diagnoses cases one day each week. Another cytologist assesses adequacy one day per week, and another cytologist stains slides one day per week. Aspirates are done only four days per week.

The laboratory has two good clinical Leica microscopes, one of which is used exclusively for screening. The other, has a photomicroscopy unit donated by Japanese benefactors. A third "adequate" microscope is set up in the ultrasonography room for immediate assessment of adequacy of fine needle aspiration biopsies. Dr. Bozhok would like an additional microscope for clinical use, especially with a fluorescence unit for special stains. I am unclear as to why the second Leica microscope is not in clinical use; it is locked in a separate room. I will look into this on my next visit.

Adequacy assessment

A cytologist assists at the ultrasound guided fine needle aspiration biopsies and assesses adequacy based on microscopic examination of unstained slides. The assessment of adequacy based on unstained slides is new to me but seems feasible after a demonstration; the condensor or diaphragm is lowered or closed. The current cytology staff appears comfortable with this approach, hence it is unnecessary to impose Diff Quik staining for the immediate assessments (the method used in the US). The only means I have to verify that this technique works is that their reported rate of insufficient specimens is in the range of 1 to 4%, which is impressively low. I have not seen whether there are specific guidelines in use for their assessment of adequacy.

Definition of diagnostic categories

It would be valuable to specify cytologic diagnostic categories and their criteria in writing.

Criteria for determining who performs the aspirate

It is my impression that only the sonographers, not the endocrinologists, perform fine needle aspirates, even if the nodules are palpable. If both are *performing aspirates, it is* important to specify how the decision as to who does the aspirate is made.

Criteria for determining surgical intervention

All detected nodules are aspirated, in spite of the fact that the protocol indicates that in adults, only nodules greater than or equal to 1.0 cm in diameter, and in children, only those 0.5 cm. or greater in diameter should be aspirated. This protocol criterion should be changed to reflect the actual practice.

It would be valuable to document the criteria used by endocrinologists to recommend surgery. Even if the decision is multifactorial, it is useful to specify the decision making criteria as it pertains to fine needle aspirate diagnoses i.e. the algorythm. It will be of interest to determine how often a second cytologic review is performed, particularly on indeterminate cases and how discrepant opinions are reconciled. The reported sensitivity of 98% is high. I assume inadequate cytologic specimens are excluded; the method of arriving at the sensitivity should be specified.

Quality Control / Quality Assurance

I doubt histologic diagnoses are used to revise cytologic diagnoses, but this would be important to know as it would change the sensitivity, specificity, positive predictive value, and negative predictative value. The negative cytologic diagnoses are not reviewed even randomly or spot checked by a second cytologist. This would be a valuable quality assurance measure. Cytologists do check the written histologic diagnosis (not the slides) and use the histologic diagnosis as a "gold standard" and as the basis for calculating sensitivity of cytologic diagnosis, a good first step toward the QA goal.

Quality assurance and quality control limit the reliability of the data. For the cohort, it will be necessary to review both positive and negative cytology cases.

Suggestions and proposed milestones for cytology laboratory (Ukraine and Belarus):

1. Create written criteria for specimen adequacy, diagnostic categories, and instructions for filling in forms. I will provide guidelines from Papanicolaou Society.

2. Create a log of cohort cases, fine needle aspiration biopsy diagnosis and histology diagnosis directly in the laboratory and in DCC.

3. Establish a system for performing and documenting secondary review of cohort cases' slides even when the initial diagnosis has been "non-informative".

4. Mention whether discarding slides is done prior to, or subsequent to, recording the number of slides.

5. Change the minimum size requirement for the FNA of thyroid nodules to reflect what is being done.

6. Clarify the role of Aksakochina in the sonographic and FNA evaluation and re-evaluation of Bel-Am cohort patients.

7. Determine the frequency with which FNA's are performed by endocrinologists rather than sonographers. Based on specimen adequacy rates: determine whether endocrinologists require additional training and/or credentialing, or whether all cohort aspirates should be done by sonographers.

Robert J. McConnell, M.D.

KYIV, UKRAINE

2 June 1998: The weather is hot, more like southern Spain than Eastern Europe at this time of year. We were met at the airport yesterday by Dr. V. P. Tereshchenko, who arranges for our transfer to the Dnipro Hotel with his usual efficiency. He looks fit and relaxed and not unhappy to see us.

Although the presentations at the International Conference at the Puzcha-Ozernaya Sanatorium are received with muted enthusiasm, the audience claps politely. Dr. Greenebaum and I meet with Dr. T. Bogdanova and discuss her study of 296 patients with thyroid cancer, which will be formally presented in Cambridge next month. These cases are taken from a group of 80,000 patients throughout the Ukraine that she has been tracking since 1986. She also has 22 cases of thyroid cancer in a Thyroid Cancer Registry culled from the smaller study cohort of 20,000 and over the last several years has been targeting thyroid pathology specifically in the Kyiv, Chernigov, and Zhytomyr oblasts. There are an unusually large number of cases of the solid-follicular variant of papillary cancer, which she has directly correlated with increasing radiation exposure. Dr. I. A. Likhtaryov, Head of the Dosimetry group, is a co-author of the study and has supplied the dosimetry data.

3 June 1998: The review of clinical operations begins with the dosimetry interviewer, Mykola Chepurny. Either the parent or the patient fills out the dosimetry forms, with default to the parent's answer (which could introduce an ascertainment bias). He feels that patients are "sick and tired" of the screening procedures and need a "motivation" to continue with the project (chairs to sit on would be nice, too). The "no show" rate is at least 25% (probably higher), but these individuals are recontacted and urged to make another appointment. Cohort members and their parents must arrange for time off from either school or work and pay for their own transportation costs, which is no small burden. Blood is obtained at the study center, but urine is brought from home. It does not bother the screeners that the urine could belong to another individual, since "everyone in the family has the same diet" (but may not take the same vitamins or medications). Although the ultrasonogram is done the same day as the initial screening, the FNA biopsy may not be. Even subjects examined by the mobile teams come to Kyiv for an FNA, since the physicians at the IEM "have the best technique." It is worth noting that the sonographers on the mobile teams are the same ones who will perform this procedure at the Institute and that the Belarussians feel comfortable with the idea of the mobile teams doing FNA biopsies.

Dr. Galina Terekova says that a major problem hampering the study is the slow "turn around" on the laboratory reports (few final endocrine forms have been processed because

of this). In all, they have seen 68 (or 72, the numbers vary) patients resettled to Kyiv from Pripyat and Chornobyl. Among these, 3 had nodules and 2 have had a FNA biopsy (the other will be seen again in 3 months). She feels that in cohort patients "all nodules are suspicious" and should have an FNA done if technically possible "regardless of rules." By this she means the Operations Manual, which states in section 5.4.1 that in patients over the age of 12, only nodules greater than 1 cm in diameter should be biopsied. The same point is raised by the Belarussians who have also adopted an aggressive stance towards smaller nodules.

Memo: (1). The need for an incentive for subjects to continue with the project is a recurring theme, both in the Ukraine and in Belarus. There are plenty of ideas about gifts (pens, tee shirts, certificates to McDonald's, etc.), but no agreement on what should be given and whether each subject should get a gift on every visit. A lottery might work, with several cohort members winning a token gift every day. This would keep costs down and interest up; (2). It should be firmly established that the FNA is done the same day as the ultrasonogram, since we could begin losing those patients who cannot return for a follow-up visit; (3). Urine for iodine should be collected at the time of the screening procedure and not brought from home (4). Although it would be best for the mobile teams to do FNA biopsies and obviate the need for subjects to come to Kyiv, convincing the sonographers to do so will be difficult; (5). The delay in processing laboratory specimens is causing distress among the endocrinologists and slowing the completion of the clinical forms; (6). I agree with Dr. Terekova that all "suspicious" nodules regardless of size should have an FNA biopsy at the discretion of the endocrinologist or sonographer. What is "suspicious" could be more clearly defined, but it might best be left "fuzzy" and leave it to discretion of the attending physicians. We could stick to the current protocol but I suspect that most nodules over 5 mm (the smallest that can be biopsied with our present technology) eventually will be sampled anyway, especially as the sonographers become more proficient and aggressive. Not allowing them to exercise their clinical judgment could result in tension, as the physicians see themselves involved in both a research project and patient care.

Met the mobile team, which has returned from the Ivankiv raion, where they spent 4 days. There are 6 "specialists" (the endocrinologist who is in charge, a sonographer, nurse, blood technician, and interviewers for both epidemiology and dosimetry) and the van driver. They examined 53 patients (out of 90 invited) and found 12 cases of thyroid pathology (9 diffuse goiters and 3 nodular goiters) and an additional patient with enlarged submandibular lymph nodes and a family history of thyroid cancer. The patients with nodules and the one with adenopathy were referred for FNA at the IEM and all were benign. The 12 "volunteers" who presented themselves for evaluation were given an endocrinologic examination and ultrasonogram, but did not have laboratory tests done. It takes about 60 minutes to complete the entire screening procedure and the feeling is that if volume increases to more than 15 patients a day "quality will suffer" (in actuality, they are capable of seeing about twice this number). Blood is obtained for both thyroid function

tests and calcium if the patient is fasting and for thyroid tests alone if they have eaten, since Dr. Ephstein feels strongly that calcium levels should be done only after an overnight fast.

Memo: It is unreasonable to expect patients to fast all morning and sometimes into the late afternoon waiting for their screening to be completed. Blood should be obtained for calcium whether the subject has eaten or not and an appropriate notation made in the record. At the final plenary session, Dr. Tronko appears to agree with this point of view.

The endocrine surgeons at the IEM have 3 computers and a computerized database of 3390 patients (90% thyroid and 10% adrenal) dating back to the early 1980s. They are eager to link their computers to the DCC, which would give us access to their records (and vice versa). We need to discuss this further.

From Dr. Yuri Bozhok, the cytopathologist, we learn that FNA biopsies are done 4 days a week, that about 2000 thyroid biopsies are done every year, and that unstained slides are immediately reviewed to ensure adequate sampling. They are not, however, working with the Cytology Forms. Finally, it turns out that there are 2 different pathology laboratories. Dr. Bogdanova receives specimens from patients under 30 years of age, while a Dr. Cherniv is responsible for the older subjects. Since the oldest cohort members are just now turning 30, Dr. Cherniv could soon begin reviewing pathologic samples from the study.

Memo: Request a meeting with Dr. Cherniv at the time of the next visit to Kyiv.

4 June 1998: Drs. Fink, Greenebaum, and I took a field trip this morning, north along the Dnipro River to Gornostaypol in the Ivankiv raion, where a mobile team headed by Dr. Bolshova, Chief of Pediatric Endocrinology at the IEM, is set up in the regional hospital. The personnel return to Kyiv every night, while the equipment remains on site. Although they planned to see only 50 patients during their 3 day visit, on the day of our visit there were 34 scheduled patients and 1 "walk in", all brought in by the van.

We are able to directly observe the screening process, following a young woman through the entire procedure. No bar codes are used on the dosimetry forms ("paper is too expensive") and, according to Dr. Bolshova, the Medical Interview Form lacks adequate space for a complete past medical history, hospitalizations, and surgeries. Dr. Yavnyuk, the sonographer, sees no need to recalibrate the ultrasound machine after moving it from the IEM, since "it is automatic." Even though he does several hundred FNA biopsies every year, he feels "uncomfortable" doing the procedure in the field.

Memo: This was a very worthwhile junket. The members of the team are friendly and enthusiastic and the patients do not seem uncomfortable with their experience. The screening process appears to be working as planned. Such trips should be done

periodically, both in the Ukraine and in Belarus. Randy Brill needs to comment on the recalibration of the ultrasonogram instrument after it is moved into the field.

At the Plenary Session, we learn from Dr. Tronko that 145 patients have been examined in the Ivankiv raion and that operations will finish there at the end of the month. On June 15, screening will begin in the Kozelets raion of the Chernihiv oblast. When Dr. Wachholz raises a point about " cross-specialty communication," Dr. Tronko gets a bit defensive, stating that it is the norm to do so "in difficult cases," which effectively ends the discussion. Although Dr. Ephstein sees no reason to do thyroglobulin measurements on all patients, after some discussion it is resolved that the final decision be "left to the USA group." Dr. Bogdanova has information of 33 thyroid cases from the last quarter, including 9 cases of cancer, but none are in the cohort. Although she is collecting data "according to the Operations Manual, she is unable to transfer data to the DCC, since she does not have the proper computer equipment. Furthermore, she is surprised that we do not have the "final" pathology form agreed to during the February visit (she was to have sent a copy to Dr. Chestvoy for comment, but he did not receive it until we gave him an English translation during our meeting in Minsk). From Dr. Markov, we learn that Dr. Oliynyk reviews "all the (clinical) forms", makes suggestions, and gives advice "for the future."

Conclusions: Although considerable progress has been made since our last visit in February and a respectable number of cohort subjects has been identified, the "no show" rate is quite high and the delay in processing laboratory specimens is a drag on progress. If it is decided to sanction biopsy of nodules larger than 5 mm in all patients regardless of age, section 5.4.1 of the Operations Manual will need to be amended. A decision about thyroglobulin assays will be needed by the next visit.

Trip Report
Kiev
June 2 to June 5, 1998

The laboratory aspects of this trip to Kiev focused on the following issues:

1. Blood collection procedures
2. Proper collection and measurement of Ionized Calcium
3. Testing required by the project
4. Progress and schedule for testing
5. Quality Control Procedures

These issues were discussed during the plenary sessions, a visit to the screening center at the institute, a visit to a district hospital where a mobile team was screening patients, and two visits to Dr. Epstein's laboratory (one with his technical staff and one with him).

Blood Collection Procedures

Nurses trained and certified by the laboratory under Dr. Epstein's direction performed phlebotomy. I observed blood drawing both at the institute screening center and at the district hospital. Blood collection was done professionally and correctly. However, at both sites, the blood was collected in a syringe and transferred to containers. This was due to a lack of heparinized vacutainers although serum separator vacutainers were available. I discussed this with Dr. Epstein; he said the heparinized vacutainers are now available in sufficient numbers and would be used beginning the week after our visit.

In general, patients bring urine for Iodine measurements to the screening center rather than collecting it during screening. I did not check to see what Instructions were given to the patients, but instructions ensure uniformity of collection, especially if a first morning urine is the desired specimen.

Proper Collection and Measurement of Ionized Calcium

Another issue that was discussed was the requirement that Ionized Calcium be collected only if the patient is fasting. Up to this point, blood has not been collected for Ionized Calcium if the patient was not fasting. This procedure was questioned by the mobile team and during the plenary session.

While it is true that the most accurate values of Ionized Calcium are obtained from a fasting specimen, there is variation from factors other than diet. Also, patients often misstate whether they have fasted or not.

After discussion, we agreed that Ionized Calcium data from non-fasting specimens was better than no data at all. Therefore, the screening process will be modified to begin

collecting blood for Ionized Calcium even if the patient is not fasting. If possible, data forms should be modified to indicate whether the patient is fasting or not.

Testing Required by the Project

The issue of what tests should be performed on every patient was discussed at the plenary session and in my meeting with Dr. Epstein. Dr. Markov had asked at the plenary session whether TG and PTH should be measured on every patient; anti-TPO and anti-TG were also mentioned.

Dr. Epstein and I reviewed the testing requirements during our meeting and agree on the following:

- Ionized Calcium and TSH should be measure on every patient
- PTH should be measured only on patients with Calcium abnormalities
- TG is not a good marker for cancer and should not be measured
- Anti-TPO and anti-TG are not required except in special cases.

I believe that TG, PTH, and the antibody tests were excluded from the routine testing called for in the study protocol in order to minimize the cost of performing the study. On a research basis, gathering information on these tests might be interesting. Therefore, it might be worthwhile to review the literature on TG and anti-TPO and to discuss this further with Dr. Robins, Dr. Mincey, and Dr. McConnell.

Progress and Schedule for Testing

I made two visits to Dr. Epstein's laboratory during this trip. During the first visit, I met with his laboratory technicians; the second visit was with Dr. Epstein.

It should be noted that no hormone testing has been performed yet for study patients. The endocrinologists expressed some unhappiness with this state of affairs and are unable to write final clinical summaries for these patients until they receive these results.

During the visit with the laboratory technicians, I discussed the routine operation of the laboratory. Dr. Epstein's laboratory measures over 30 different hormones and proteins including T_4, Free T_4, TSH, T_3, T Uptake, and anti-TG. Although the laboratory has a chemiluminescence instrument, it is not used for routine testing because reagents are too expensive. The laboratory performs mainly RIA tests using manual pipetting with Eppendorf precision pipettes, separation, and counting on a Beckman gamma counter connected to a computer for data reduction. This methodology is still used in many US laboratories but it is older technology that is disappearing in the US.

Common assays such as TSH or T_4 are run every other day in batches of 60 – 70 patients. Standards are run in duplicate but patient specimens are run only once. Results are generated by the computer and transferred manually to reports. Control material from kits or frozen patient specimens are run for quality assurance purposes

but there is no systematic monitoring of the results. Normal values have been assigned to the hormones measured in the routine laboratory by running approximately 80 normal patients. This used to be easy using military recruits but is more difficult recently.

In terms of the study, the plan is to use chemiluminescence assays. The manufacturer of the chemiluminescence analyzer is coming soon to service the instrument in the laboratory. No testing has been performed yet for hormones or antibodies because of reagent issues. The current plan is to begin testing in September. One issue is that Immulite reagents for 1000 assays have been delivered but are not being used. Dr. Epstein may be planning to discard these reagents since they are no longer being manufactured. Arrangements have been made to purchase Brahams reagents that will start coming in September.

Ionized Calcium and urinary Iodine testing has been performed on the specimens received to date. Of note is that the laboratory now thinks that the ionized calcium measurements should be done in the main lab because there is only one analyzer and it is felt that the analyzer does not travel well.

The computer program to enter data has not been tested yet.

Quality Control Procedures

There is no systematic program for monitoring the accuracy and precision of testing. Frozen patient specimens are run with each batch of routine specimens and the results reviewed. If the variation from the previous value is too large, (?10 percent). the results are reviewed. However, no records are kept of this process and no data is collected on accuracy and precision. For any given assay, this cut-off may be either too narrow or too wide to be of much use, and instead, should be set for each assay specifically.

I brought three papers on laboratory Quality Control for Dr. Epstein (they need to be translated) and reviewed with him the basic concepts. We discussed the use of Levy-Jennings plots of QC results to identify results that might represent analytical failure *and require intervention*. This identification is based upon a rule set of quality control rules. We went over the simplest 3 SD rule but also discussed the more complicated Shewart rules. Dr. Epstein seemed quite interested in this approach and said he would set this up as soon as feasible. I suggested that he Email or fax me if he had any additional questions or if questions arose during implementation.

Finally, we discussed exchanging unknown specimens. He would be eager to receive unknown specimens from either a laboratory or a proficiency testing program. We discussed whether there would be customs problems and he said he would investigate. We agreed I would try to send him specimens before my next visit.

Visit to Minsk, Belarus - June 8, 1998 to June 10, 1998

III. STUDY OF THYROID CANCER AND OTHER THYROID DISEASES IN BELARUS FOLLOWING THE CHERNOBYL ACCIDENT

Dr. V. Stezhko, Director of the Project and Head of the Department of Ministry of Public Health chaired three plenary sessions involving all senior staff of the BelAm project, NCI staff, NCI consultants and the Columbia University contract personnel. My comments and suggestions detailed below are primarily limited to the meetings I had with Dr. Elena Buglova, Head of the Epidemiology Group and her two colleagues Dr. Ludmila Kul'kova and Dr. Alexander Skalizhenko, Mr. Artur Kuvshinnikov, Head of the Data Coordinating Center and Drs. Gil Beebe and Herman Mitchell.

A. Background:

A cohort of approximately 15,000 children (18 years of age or younger at the time of the Chernobyl accident) who had dose measurements taken in 1986 has been identified in eight oblasts of Belarus, including the city of Minsk. This file, which is often referred to as the Moscow file is made up of 8500 children with high doses, and 7500 with medium or low doses. At the time of my first trip to Minsk, Belarus in February of this year, current addresses of approximately 8500 (60 percent) of the cohort had been determined through a combination of two methods i.e. linking the dose measurement list (the Moscow list) with the Chernobyl Registry and through the Chiefs of Medical Structure at the raion level (manual searches of local medical record departments of dispensaries and outpatient clinics).

Letters introducing the study to potential cohort members had been sent to those with known current addresses resulting in 2200 who provisionally agreed to participate with another 6200 unknown status or refused. The great majority of the 6200 with unknown status were potential cohort members who did not respond in any way to the invitation letter or who responded indicating that they could not participate for a number of reasons. A high proportion of this group of cohort

members could include persons with incorrect addresses, but this cannot be confirmed. The absolute refusal rate was approximately 10 percent.

In addition, approximately 3500 of the original 15,000 cohort members had been set aside for consideration later due to the fact that the identifying information on the measurement file (the Moscow file) was considered inadequate for matching to the Chernobyl Registry.

B. June 8, 1998 to June 10, 1998 Meetings with Drs. Beebe, Buglova, Kul'kova, Mitchell, Skalizhenko and Mr. Kuvshinnikov

① Establishment and Ascertainment of the Cohort Including Follow-up: Dr. Buglova indicated that only 29 percent of potential cohort members to date have been found by linking the dose measurement file with the Chernobyl Registry and that the linking with other files, e.g the Bureau of Addresses Ministry of Internal Affairs, the Office of Technology and the Ministry of Emergency has been problematic.

SUGGESTION: It was suggested that Dr. Howe's probabilitistic record linkage system would be invaluable in improving the linking of the above noted files. The possibility that computer matching may be improved by this superior linkage software was discussed and in this context Dr. Howe has offered to conduct a training workshop in Kiev at the Chernobyl State Registry utilizing practical ready made software to conduct linkages. Since linkage between data sources is somewhat questionable in all three studies (i.e., leukemia/lymphoma cohort of clean-up workers, thyroid in children studies in both Ukraine and Belarus), I would suggest that the personnel who would actually carry out the day to day linking of these files in all three studies attend this workshop in Kiev. Improved record linkage would also undoubtedly improve the linking of the 3500 member cohort (set aside because of inadequate identifying information) with the Chernobyl Registry

Since my first trip to Minsk in February of 1998 the BelAm project has evidently "confirmed" the addresses of approximately 42 percent of the original 15000 cohort by expanding the sources used to identify up to date address information from the manual searching of medical records at the local area and linking the dose measurement file to the Chernobyl Registry to other sources such as the Ministry of Internal Affairs (Bureau of Addresses) among others.

At the time of our meetings, however, Dr. Buglova was unable to tell us the exact numbers in various sub-categories of search mechanisms. The best estimate that I could come up with is that, of the total number of potential cohort members found with up to date address information, 25 percent were found by the searching of local medical records, 29 percent were found via linkage with the Chernobyl Registry, 33 percent were found through the Ministry of Internal Affairs (actually through the Bureau of Addresses which evidently receives information from the passport offices at the oblast level), and 10 percent from other sources.

Additional sources which have been approached include the school system, the Office of Technology at the national level and the Ministry of Emergency. The school system was found to be of little use since there are no centralized records. The Office of Technology evidently identified only 50 possible cohort members out of a list of 900 children who were found to be in the correct age range, and the results from the Ministry of Emergency to date suggest that this source is only available for children who were evacuated or re-located to Modilov oblast.

SUGGESTION: I have been quite impressed with the tenacity with which the epidemiology group in the BelAm project has approached other data sources as alternative means of identifying potential cohort members and would suggest that this is continued especially in regard to the Bureau of Addresses/Ministry of Internal Affairs.

SUGGESTION: In order to facilitate continued follow-up of cohort members who are currently being entered into the study it is essential (as I mentioned in my first trip report)

that thank you letters be sent to individuals following their attendance at screening and interviewing. It is my understanding that, owing to some friction between the epidemiology group and the DCC, this has, in fact, not been done for those recruited to date.

② In utero study: Dr. Buglova briefly described the work to date in the in utero study. A list of all births in Belarus from April 26, 1986 to January 31, 1987 has been obtained and, on an on-going basis, is being entered into a file which ultimately will be linked to the dose measurement file (the Moscow file). This list includes identifying information about the natural mother, information on the birth, e.g., date, gender of child, outcome (i.e., live birth or stillborn), and address of hospital. Evidently, approximately 100,000 are on this list of which 11,000 (all in the city of Minsk) have been data entered.

SUGGESTION: At the completion of this data entry of the birth list, the linkage between this file and the dose measurement file would be facilitated by the utilization of probabilistic record linkage and by the attendance of those to be involved in this linkage at the suggested record linkage workshop to be held in Kiev.

③ Fieldwork: A total of 4,770 potential cohort members were sent a letter inviting them to participate in the study with the result that 3,576 agreed to participate (by sending in postcards saying they would participate, telephoning in their responses, relaying their intent to participate at the local level through medical personnel). Of those that agreed to participate following this initial letter, 2,692 have been recruited, interviewed and examined. Evidently, the number of recruited and examined cohort members includes 1,820 who are resident in Gomel, of which only a fraction were recruited and examined by the mobile team. The number of refusals is evidently quite small in all study areas.

SUGGESTION: At the present there is in fact little or no documentation of the procedures being used to trace and recruit potential cohort members and success rates for these various

procedures. Furthermore, at the time of our meetings there appeared to be a major problem (depending on who you listen to) with the Data Control Center in terms of entering forms which do have some documentation and then retrieving information back from the DCC. Together with Drs. Beebe and Mitchell a suggestion was made that an administrative file be created for tracking the progress of the cohort from selection through to the various steps in the screening process. At the time of our meetings, Mr. Kuvshinnikov provided us with a copy of the current database that could be modified for this purpose. Dr. Mitchell sketched out a flow chart that represents the kind of information that would be needed and it is my understanding that once this has been refined it will be sent to the BelAm group.

At the time of the meetings in Belarus we had hoped to meet with the mobile team and learn of their experiences in the field as we had been given the opportunity to do so in Ukraine but this did not happen. However, in discussions with Dr. Buglova, several points were raised regarding on-going fieldwork, including the work of the mobile team.

SUGGESTION: First of all I was encouraged to learn that subsequent to my first trip to Belarus in February of this year that the invitation letter to potential cohort members was changed to become more "user friendly. However, letters of invitation should be more specific in terms of what they require of the respondent, e.g., a fasting blood is one example. The invitation letters should indicate that the parents of the child (or some other person) who knows the most about the child at the time of the accident) be responsible for filling out the questionnaire. Additionally, it is absolutely essential that the BelAm forms be changed to indicate who answered which questions or alternatively who answered most of the questions. Also, in order to eliminate questionable data from analysis it would be a good idea to have the interviewers at the time of screening evaluate the reliability of the respondents' answers.

④ Development of Coding Manuals: Evidently, despite the fact that examples of how to fill in forms and appropriate codes are delineated in the Operations Manual there are major problems

in completion of forms, and ultimately this has compounded the lack of any data entry of the medical data from the screening process and quality assurance/quality control.

SUGGESTION: It is absolutely essential that a coding manual be developed as soon as possible for all forms that are filled out at any time during the progression of the study. This manual must have in it practical suggestions and examples of how to and how not to fill in data fields as well as explicit codes that can be filled in. Only when this manual has been completed and explained to the various personnel who actually fill in the forms can any attempt be made at quality control and viable data entry. In this regard, two milestones have been suggested for the third quarter: Milestone 7 "Draft Instructions for Filling Out All Study Forms" and Milestone 8 "Draft a Coding Manual for Coding the Study Forms" The compilation of a coding manual for all forms in the study should in fact include instructions for filling out forms.

It was learned at the time of our meetings that the BelAm project is expected to hire Dr. Olga Polyanskay to coordinate quality assurance/quality control as well as updating the Operations Manual. I cannot emphasize too strongly that if she is hired that one of her first tasks should be the compilation of such a manual and the monitoring of form completion/questionnaire administration adhering as strictly as possible to the codes which are pre-assigned on all forms and the instructions as to how forms and questionnaires are completed.

⑤ Equivalence Between Ukraine Thyroid Study and Belarus Thyroid Study: In my first trip report I commented on the need to ensure that the study procedures and data forms in the two studies be as similar as possible so that at the conclusion of fieldwork the two data sets could be combined for data analysis if deemed necessary.

During our meeting, it became evident that there are, in fact, some differences between the two studies. In the Ukraine study, the dosimetry questionnaire is completed by the cohort member at the

time of examination or subsequent to this, by a parent, etc., if the cohort member is of the age that he/she cannot recall events circa April 1986.

In the Belarussian study, it seems two questionnaires, although basically identical, are completed. A self-administered dosimetric questionnaire is sent with the invitation letter to the potential cohort member and he/she then is requested to bring that completed form to the clinic at time of screening. Then the second questionnaire is administered to the cohort member or completed subsequently by the parent and sent back to the clinic. I am somewhat concerned about the equivalence of the dosimetric information between the two studies as it appears that the ascertainment of dosimetric information in Belarus is much more intense than that in Ukraine. In this regard, although the Belarus questionnaire asks the same basic questions as does the Ukraine questionnaire, the former includes many more additional questions.

SUGGESTION: Wherever possible, the questionnaires and the introduction and administration of these questionnaires to cohort members should be identical in both studies.

C. Overall Impressions:

In general I was very encouraged by the work of Dr. Buglova and her group especially with regard to the success they have had in tracing the number of potential cohort members they have and their tenacity in doing so. I was, however, dismayed at the seeming lack of documentation at all phases of the study which would enable the investigators and ourselves to assess accurately progress to date and to evaluate the various mechanisms of cohort identification and recruitment. It is essentially this lack of documentation and monitoring that has compounded the problems associated with data entry and quality assurance/quality controls.

Date: Mon, 29 Jun 1998 07:31:09 EDT
From: EGslowski@aol.com
To: jdb32@columbia.edu
Subject: kiev-ellen greenebaum

TRIP REPORT TO KIEV AND MINSK - JUNE 1998

Ellen Greenebaum, M.D., Senior Cytopathologist, New York Presbyterian Hospital, Associate Professor of Clinical Pathology, College of Physicians and Surgeons, Columbia University

MINSK: BEL-AM PROJECT

Cytologists in Minsk are biologists referred to as Laboratory Doctors, as in Kiev. There is one cytologist involved with the cohort study, Dr. Yelena Kapanovitch. Four other "thyroid experts" with the same "U.S. cytotechnologist" level training also work at Dr. Dmidchik's laboratory. I did not meet the other 4, but I was told that they were all "senior." They are all at the same level without a designated cytology supervisor; Dr. Dmidchik, a surgeon, is the professional in charge.

Thus far there have been 9 fine needle aspiration biopsies, consisting of 42 slides, on cohort children. I believe these slides are all from Minsk, but do not know how many were repeated in, or derived from, Aksakachina. Also, these case and slide numbers may include patients screened now, but with prior FNA'S dating back to 1995. I need information regarding the cytology program at Aksakovchina.

Will all cohort patients with nodules detected now, and with a history of fine needle aspiration in the past, need slide review and a form?

No pathologist has reviewed or is involved in assessing the cytology material. No followup is performed by the cytologist or pathologist as to the diagnosis of the other's pathomorphologic studies. No calculation of sensitivity or positive predictive value is being performed. No review of negative cases is performed. Review of even a sample of negative cases would be a good quality assurance measure. No report of percentage inadequate cases is given. No written criteria for diagnostic classification has been made available to me. No cytologist is available for immediate assessment. This is a problem according to the ultrasonography doctors and endocrinologists. I am not sure whether endocrinologists sometimes aspirate palpable nodules. It seems that the endocrinologists and ultrasonographers want to be able to assess adequacy themselves, the implication being that the adequacy rate is low.

The ultrasonographers and endocrinologists asked for a cytology presentation from me on future visits to discuss assessment of adequacy, what the cytologist can and cannot tell, and basic cytodiagnostic criteria for thyroid cancer.

I need approixmately 2 full days to review cytologic cases, including both negatives and positives among cohort patients, to assess the quality of the fine needle aspirations and aspirators. Before this occurs it is necessary for me to have the cohort's diagnostic forms translated into English- including diagnoses, conclusions, and histopathologic diagnoses- before my arrival, in writing. This would also allow me to determine whether the cytologist is using the forms correctly, enabling me to get and give feedback as to whether the forms are appropriate, prior to the 1 year cut-off point for the alteration of forms.

It would be valuable for me to visit Aksakachina or to at least find out its role in the cytologic workup. I am interested to find out the validity of the complaint attributed to the doctors in Aksakachina that fine needle aspirations should not be done anywhere besides there!

Suggestions and proposed milestones for cytology laboratory (Ukraine and Belarus):

1. Create written criteria for specimen adequacy, diagnostic categories, and instructions for filling in forms. I will provide guidelines from Papanicolaou Society.

2. Create a log of cohort cases, fine needle aspiration biopsy diagnosis and histology diagnosis directly in the laboratory and in DCC.

3. Establish a system for performing and documenting secondary review of cohort cases' slides even when the initial diagnosis has been "non-informative".

4. Mention whether discarding slides is done prior to, or subsequent to, recording the number of slides.

5. Change the minimum size requirement for the FNA of thyroid nodules to reflect what is being done.

6. Clarify the role of Aksakochina in the sonographic and FNA evaluation and re-evaluation of Bel-Am cohort patients.

7. Determine the frequency with which FNA's are performed by endocrinologists rather than sonographers. Based on specimen adequacy rates: determine whether endocrinologists require additional training and/or credentialing, or whether all cohort aspirates should be done by sonographers.

Robert J. McConnell, M.D.

MINSK, BELARUS

8 June 1998: During the agenda session, we learn from Dr. Stezhko that Dr. Yuri Dimidchik has assumed the post formerly occupied by his father as head of the Thyroid Surgery Center at the Minsk Medical Institute. The senior Dimidchik, now retired from surgery, is heading the Tissue Registry at the Institute of Radiation Medicine and Endocrinology.

Almost 800 visits by cohort members have been recorded for the first 5 months of this year, including 69 patients from Bragin and 127 follow-up appointments. A mobile team worked for 4 days and identified 5 patients (2 new) with nodules, but FNA biopsies were not performed since the older Sigma ultrasound machine could not adequately image the entire gland. Although the subjects were referred to the Aksakovchina Clinic for further evaluation, the 2 patients with new nodules "disappeared," underscoring the necessity to biopsy nodules when they are discovered and not expect patients to return for another visit.

There is a "data flow problem" between the Dispensary and the DCC which threatens the entire operation. Ultrasound, Palpation, and Preliminary Medical Screening forms are not being sent in a timely fashion and the final medical screening forms are not being sent at all. This has lead to considerable tension between Dr. Rzheutsky and Arthur Kuvshinnikov and it soon becomes obvious that they dislike each other intensely. Dr. Stezhko sides with Dr. Rzheutsky, saying that he "needs support", which translates into: (1). A new copying machine to facilitate the transfer of paper forms to the DCC (It is agreed that the originals should stay at the Dispensary and be available for patient care. Gil Beebe makes the point that "there is too much paper already" and the emphasis should be on electronic data transfers); (2). A second computer operator (even though the one he already has does not work full-time on data entry and devotes some of her time to other clerical matters); (3). The "final" version of the data-entry software (a point forcibly disputed by Kuvshinnikov); (4). A new Tosbee 240 ultrasound machine for the mobile team.

It was pointed out by Dr. Stezhko that "our experience shows that we have many problems with forms" and that "perhaps we should review them more carefully," even though it was previously agreed to use the forms for a year before discussing changes. Dr. Khlyavich, one of the sonographers, and I subsequently reviewed the Ultrasound Examination Form and the changes he proposed were reasonable. He wished to add a category for "Minimally abnormal thyroid" under section 8 and delete "Slice ID" on the last page, since it is "never used."

The Dispensary is moving, with a complete transfer of clinical operations to be completed by mid-July. The new facility is located on Makaenka Street, about a kilometer from the nearest metro stop. Screening will continue throughout the summer, with a projected volume of about 30 subjects each day. The laboratory will be relocated after more extensive renovations to the new building, a delay which could further retard an operation which is seriously lagging in processing the specimens already collected.

Dr. N. Litvinova, an Endocrinologist at the Dispensary, tells us that in 757 patient visits (2 were follow-ups) during the first quarter of this year, thyroid abnormalities were found in 97: 11 cancers (4 new), 43 nodular goiters (31 new), 6 chronic thyroiditis "confirmed" (with an additional 10 "suspected"), and 27 diffuse goiters (21 WHO class IB, 5 class II, and 1 class III). FNA biopsy was performed in 9, 22 were referred to the Aksakovchina Clinic for further evaluation, and 6 sent directly to Dr. Y. Dimidchik for surgery (of the 5 operated upon, 4 were cancers and 1 was a benign adenoma).

The relationship among the Dispensary, the Aksakovschina Clinic, and the Thyroid Surgery Center is complex, but is at least partially clarified by Dr. Larissa Danilova. Not every patient with a suspected malignancy is referred to the Clinic, since ones with highly suspicious cytology may be sent for immediate operation. By decree of the Ministry of Health, an "Oncologist" decides which patients go to Aksakovschina for further evaluation. Otherwise, it is implied, more patients would be taken directly to surgery, since the surgeons are "aggressive."

Dr. Y. Dimidchik proposes making changes in the Hospitalization (Surgery) Form to allow addition of a second surgical procedure and multiple doses of radioactive iodine, both of which are appropriate. He also wishes to "link" with the DCC and begin a long-term follow-up of his cases. Although postoperative outcomes are not part of the current study, I feel that much useful information could come of it.

Dr. Khlyavich tells us that, contrary to the Operations Manual, FNA biopsy is done on most nodules over 5 mm in diameter. He also is of the opinion that FNA can be done by the mobile teams once an appropriate ultrasound machine is obtained (the Tosbee that Dr. Rzheutsky covets). They are having a problem insuring that aspirated specimens are adequate for cytological interpretation, since Dr. E. Gapanovich, a cytopathologist based at the Thyroid Surgery Center, reviews slides only part-time at the Dispensary. Unlike the setup in Kyiv, slides are not reviewed at the time of biopsy, so patients sometimes need to return for another procedure. Color doppler is done on "difficult cases and pathologic glands," but there is no obvious record keeping. The Aksakovschina Clinic also has a color doppler and has been using it for the last few months.

Memo: The sonographers could be taught to review slides, obviating the need for a cytopathologist to be in attendance. This would also be a useful skill for the mobile teams to have, cutting down on the number of referrals to the Dispensary and reducing the need

for return visits. It would be necessary for them to receive the proper instruction in slide review and to have a microscope ("Dr. Rzheutsky will not give us one").

9 June 1998: After Dr. Rzheutsky makes his pitch for a calcium autoanalyzer to take into the field, Dr. Fink points out that Dr. Ephstein found that "the autoanalyzer did not travel well." The counter-argument is that "the specimens do not travel well" and only stay frozen for 6 hours, too short a time to transport back to the Dispensary. No final decision is reached and the discussion stops here. Dr. Rzheutsky plans to employ 3 endocrinologists full time: 2 at the Dispensary and 1 on the road. If the volume of patients increases (and if funding is available), he would add yet another endocrinologist at the Dispensary and organize a second mobile team. He anticipates that the mobile team will be able to screen 20 patients a day and be away for 10 working days each month. For "walk in volunteers," he plans to examine them ("it is impossible to refuse") and either not use the data or check with the DCC to see if the patient can be included in the study.

10 June 1998: This morning we had a chance to visit Dr. Yuri Dimidchik at the Thyroid Surgery Center. Although he gets most of the thyroid cancers in Belarus, a "small number" are operated upon in the oblasts (Dr. Cherstvoy claims that Dr. Stezhko has information about how many). Although patients are generally filtered through the Aksakovschina Clinic, those from Mogilev are sent directly for surgery. The Center does almost 1200 thyroid operations a year, for both benign and malignant disease. They run 3 operating rooms (2 tables in each) and have about 60 thyroid cases "in house" at any one time. There are facilities for FNA, cytopathology (Dr. Gapanovich), pathology (Dr. Siderov), and a storage facility for tissue blocks dating back several years.

After a tea break with Dr. Dimidchik, we were driven across town to see Dr. Cherstvoy, who has sufficiently recovered from his stroke to meet with us. He had just received the English translation of the Ukrainian pathology form, faxed to him from the DCC the evening before. His strong feeling was that there were "too many extraneous items not useful for the project." Although he did not elaborate on this (and I did not feel free to press him for specifics), he did agree to discuss the matter further with Drs. Bogdanova and Virginia LiVolsi in Cambridge. He further proposed that the expert pathology group convene in Minsk, since "it would be simpler." He reviews the pathology for all patients up to age 20 (and all "complicated" cases regardless of age) and has tissue blocks and frozen sections dating back to 1991 (he would like all pathologic material stored at his facility instead of sharing it with the Thyroid Surgery Center). Unlike Dr. Bogdanova, who is finding a huge increase in the solid-follicular variant of papillary cancer, he finds "no special radiation effect" in his material. He has also reviewed Ukrainian specimens and finds "mistakes."

At the concluding Plenary Session it is agreed to change the Operations Manual to allow FNA biopsy of all nodules greater than 5 mm in size. It is apparent that translation must be done between the old and new WHO classification of goiters, since Arthur Kuvshinnikov

has almost "6000 patients" in his data base according to the old grading system and it seems useful to begin classification according to the new one. It would also be prudent to keep the written description along with the WHO Grade (e.g., Grade 0 = no palpable or visible goiter).

Conclusions: The clinical screening is moving ahead at a steady pace, but a bottleneck has developed in the flow of data between the Dispensary and the DCC. As in the Ukraine, the Operations Manual (section 5.4.1) would need amendment to accommodate biopsy of nodules larger than 5 mm. We should directly observe operations of a mobile team "in the field." Dr. Y. Dimidchik is establishing himself as an important member of the project and we should develop a good relationship with him.

Minsk
June 8 – June 10, 1998

During our visit to Minsk, the following questions were raised and discussed either in plenary sessions or in meetings with the laboratory staff:

1. Test results to date
2. Reagent purchasing issues
3. Need for TG, anti-TG, anti-TPO, and PTH
4. Continuation of Iodine measurements after first screening
5. ICA storage conditions
6. Quality Control
7. Broken analyzer
8. Move of laboratory

During our visit, I met with Dr. Petrenko in two long and one brief session to discuss laboratory issues. These issues also came up in various group and plenary sessions.

Test Results to Date

The examination of blood and urine specimens is going slowly. Blood and urine has been collected on about 1,550 different patients in 2,692 screening visits since 1996. To date, urinary Iodine determinations have been done on most of these specimens but Ionized Calcium and TSH have been performed only on the patients screened in 1998, approximately 600 patients. Antibody studies have not been performed on any patients. There are over 2,000 frozen specimens awaiting analysis. I suggested that a milestone be added to catch up on the testing over the next 1 or 2 quarters. Also, data entry programs have just become available and have not been tested.

Dr. Petrenko reviewed the results of urinary Iodine testing with me. The average values varied considerably from Oblast to Oblast with the highest values seen in Minsk and Gomel Oblasts, presumably because of better diets. Of some concern is that values on repeat patients varied considerably from year to year, and the average values for the Oblasts also varied greatly (+64% to – 25%) from year to year. There are three possible explanations for this. First, in a small series of experiments, first morning urinary Iodine varied considerably from day to day based on diet. Second, there was a calibration problem early in the study that may have altered the results of patients studied early on. Third, patients were bringing the urine to the screening so the conditions under which it was collected may not have been uniform; perhaps a 24-hour urine would give a more accurate result.

Reagent Purchasing Issues

Dr. Petrenko complained of slow arrival of reagents. However, a review of orders with Dr. Masnyk showed that all requested reagents had been ordered and scheduled for delivery. To date, 600 TSH tests from Abbott have been received and run. A total of 1800 more TSH tests will be received by October. In addition, Brahams reagents for anti-TG (1000), anti-TPO (1000) and PTH (100) have been ordered and scheduled for delivery in the next 6 weeks. These are radioimmunoassay tests with a shelf life of 2 months. How to use these reagents and the impact of the impending move on these reagents will be discussed below.

Need for TG, anti-TG, anti-TPO, and PTH

The need for additional testing was discussed. There have been repeated suggestions by individuals that these assays be done more frequently than was contemplated. At first glance, it would seem that these tests are adjuncts and the expense of trying to do them for a significant number of patients would be too high. It has been suggested that they be run based on clinical or laboratory indications or that they be run on a fixed percentage of patients. Since we are not sure of the clinical usefulness of these tests, targeted testing might be worthwhile. Patients with the 5 % highest and 5 % lowest TSH values would be tested for these analytes to see if there are any correlations between disease and these parameters. In addition, all patients with nodules and or carcinomas should be tested. These matters will be reviewed when we return home and a final recommendation made to the advisory committee.

Continuation of Iodine Measurements after First Screening

It was envisioned that Iodine testing would be stopped after an initial screening period of 1 or 2 years. However, the variability in the results to date suggests that this be re-examined. We need to determine if the variability is due to the mode of collection or some other factor such as the calibration problem noted early on in the study. I would suggest we await more results, review the literature on this testing, and discuss it further on our next visit in order to make a recommendation to the advisory committee.

iCa Storage Conditions

Given that there is only one iCa analyzer, it must remain at the institute. Furthermore, the Ukrainians have found that it does not travel well. However, Dr. Petrenko feels that iCa is not stable, even when frozen, based on a small series of experiments that he has done. Furthermore, he is concerned that the long trip back from the field to the laboratory will make it impossible to maintain frozen conditions. His findings are at variance with my impressions and I will review this issue in the literature before the next visit.

Quality Control

Although reference urine is run with urinary Iodine tests and Abbott controls are run with TSH tests, Quality Control is not approached in a systematic fashion and accuracy and precision are not tracked. In the case of urinary Iodine testing, the technicians run

a reference serum with each batch. However, each technician maintains his/her own reference pool and there is not a protocol for monitoring or reacting to outliers. In at least one case, an outlier was generated but no action was taken.

This finding led to a discussion of the Quality Control literature I had brought for Dr. Petrenko. We discussed the general approach to Quality Control and I showed him with graphical illustrations the basic ideas behind this approach. The key concepts discussed were Levy Jennings charts and the Shewart rules for detecting outliers. These concepts are described in the procedure manual developed for the laboratory by Dr. Mincey. However, the concepts and their implementation had not been discussed with Dr. Petrenko so he had never attempted to implement them. He said that our discussion and the documentation I gave him give him a basis for using these techniques; he stated that he intends to implement these techniques into his routine testing procedures.

Finally, we discussed the issue of exchanging unknown specimens. He would be eager to receive unknown specimens from either a laboratory or a proficiency testing program. We agreed I would try to send specimens to him before my next visit.

Broken Analyzers

On the last day of our visit, we learned that the Abbott TDx analyzer had broken the previous afternoon. Dr. Petrenko and I looked at the instrument. The stepper screw that controls the motion of the reagent probe is broken. No testing can be done until this is repaired. Abbott has a repairman for Minsk but a mechanism of payment must be established. If the instrument was acquired as part of a reagent rental contract, maintenance is covered at no additional charge. However, the exact method of acquisition was not known at the time of the visit and would have to be determined.

There has also been a broken component on the gamma counter for 2 years and repair has not been performed. The project must establish a general approach to maintenance issues.

Move of the Laboratory

The move of the dispensary will have a negative impact on laboratory testing. The laboratory will have to move twice because the renovations in the new dispensary will not be completed before the laboratory has to move out of the old dispensary. Furthermore, the interim space is not good laboratory space and may not be suitable for testing, much less RIA testing.

Dr. Petrenko will have to suspend testing while these issues are resolved and a new RIA permit issued by the government. Furthermore, the recently ordered RIA test kits have a shelf life of 2-3 months and if testing is suspended, these kits may expire unused. A delay in shipment is probably required.

Finally, all the frozen specimens must be moved without thawing or other damage.

APPENDIX 2

Draft Protocol for Review of Random Sample of Previously Diagnosed Cases with Leukemias, Lymphomas and Related Disorders in Ukraine

PROTOCOL FOR REVIEW OF RANDOM SAMPLE OF PREVIOUSLY DIAGNOSED CASES WITH LEUKEMIAS, LYMPHOMAS AND RELATED DISORDERS IN UKRAINE

A. Introduction:

In order to determine whether or not diagnoses of leukemia and lymphoma can be ascertained both in the past and future through existing clinical and biological material available in Ukraine it is planned to engage a diagnostic review panel of hematologists/pathologists to review a random sample of previously diagnosed patients.

The random sample will be chosen from all patients diagnosed from 1987 up to and including 1997 in all oblasts and study areas which will be included in Phase II of the study. These are the oblasts of Dnipropetrovsk, Donetsk, Kharkiv, Kiev and Sumskaya and the city of Kiev. The epidemiology group under the direction of Dr. Natalia Gudzenko will proceed as soon as possible to obtain lists of both deceased and living cases diagnosed with leukemias, lymphomas and related diseases in the above listed areas in order to subsequently choose from each area a random sample (based on different diagnostic categories among male cases in the defined age group 20 to 40 years old at the time of the Chernobyl accident). The sample will be chosen from lists of all cases diagnosed with leukemias and lymphomas and related diseases maintained by central oblast hospitals, oncology dispensaries or city hospitals. The appropriate senior medical director at each institution will be approached to expedite access to these lists and the obtaining of the relevant clinical and biological material for those cases who are subsequently chosen for the random sample by type of diagnostic classification.

B. Sources in Ukraine for Determination of Patients Diagnosed With Leukemias, Lymphomas and Related Disorders:

In consultation with Drs. Dyaghil, Gudzenko and Klimenko it was determined that the major sources of information on retrospective cases of leukemia, lymphoma and related disorders are:

① For leukemia cases in Ukraine, the hematology departments in either a single city hospital or oblast hospital outpatient clinic where all cases with leukemia are routinely followed are the major sources of identification.

② For lymphoma cases the major source within the oblast and the city of Kiev will be the oncology dispensaries.

For both sources ① and ② combined, it is estimated that no more than 12 separate institutions and/or departments will need to be contacted.

③ City and oblast hospital morgues.

④ The State Chernobyl Registry of Ukraine which keeps data on yearly medical examinations of all persons registered.

⑤ The Bureau of Lifetime Events (Ministry of Population Statistics?) which maintains updated information on lifetime events such as births, marriages, and dates and causes of death for all Ukrainian citizens.

C. Most Appropriate Source for Diagnostic Review:

For the purposes of the diagnostic review it was determined that the most appropriate sources in terms of the basic goals of the review and its practical implementation are:

① For leukemia cases, the hematology departments/outpatient clinics of the oblast hospital and/or city hospital; and

② For lymphoma cases, the oncology dispensary for each oblast and city area.

D. Reasons for Selecting Sources A and B as the Most Appropriate Sources for Purposes of Diagnostic Review:

① In accordance with the organization of medical services in Ukraine all patients who are suspected of having leukemia or lymphoma are directed by their physicians to the hematology department of either the oblast or city hospital. In the case of treatment for patients with suspected leukemia who are subsequently confirmed to have leukemia, all (i.e., 100 %) have such treatment at these hematology departments. Therefore, all medical records and biological material pertaining to each such case is stored in this department.

② As per the situation with leukemia, all cases with suspected lymphomas are registered in the oncology dispensary of the oblast in which they reside. For patients who are confirmed to have lymphomas, treatment takes place either at the hematology department or the oncology dispensary of each oblast. All medical records and biological material for lymphoma cases is stored at either of these services.

E. Reasons For Not Utilizing the Other Sources:

① It was agreed not to utilize the morgues of hospitals since the autopsies performed at these institutions would identify only those additional cases with leukemia/lymphoma and related disorders who were not detected through the hematology or oncology services and who died in hospital after or during treatment for diseases other than leukemia/lymphoma. It is estimated that such an occurrence would be rare.

② The major reason for not identifying cases with either leukemia or lymphoma from the Chernobyl State Registry is that this registry only includes the population affected by the Chernobyl accident. As the basic purposes of the diagnostic review are to confirm retrospective diagnoses and to assess the feasibility of obtaining the requisite clinical and biological material to do so, it is not necessary to limit the diagnostic review to this special population. If we were to obtain lists of

cleanup workers diagnosed with leukemias and lymphomas from the Chernobyl State Registry this would involve many more steps in case identification and procurement of clinical and/or biological material for review than if we utilize the hematology departments and oncology dispensaries of the study areas. Additionally, it would be impractical at this time to ask Dr. Cortushin to search his file for clean-up workers with a specified list of diagnoses made in the specified geographic areas.

NB. It is important to state that the general population of Ukraine suspected as having leukemias, lymphomas or related disorders and subsequently confirmed as having these diagnoses, are not treated in any way differently than those diagnosed with these diseases emerging in the population affected by the Chernobyl accident (i.e., cleanup workers). However, if the underlying records sought from each hematology and or oncology service contain information that indicate that the patient is a clean-up worker this information will be noted for that case.

F. Procedures to be Followed in Obtaining Case Lists From Oblast/City Hospitals:

① Dr. Gudzenko believes that at the present time the lists of cases diagnosed with leukemias, lymphomas and related disorders are immediately available for all the relevant oblasts and the city of Kiev.

② It is suggested, first of all, that a senior scientist in the project, possibly Dr. V. Bebeshko, contact the relevant hospitals and alert the key people at these institutions as to the study's request for diagnostic information and clinical/biological material. Subsequently Dr. Gudzenko will telephone the appropriate staff at each hospital so that she or a suitable delegate could visit the hospitals to examine their records. Dr. Robert Reiss (hematology and pathology), of the Columbia scientific support team, has offered to visit some of these hospitals during his next visit, possibly scheduled for September/October of this year. As noted above, it is anticipated that no more than 12 such institutions will need to be contacted.

③ The lists of cases diagnosed retrospectively with leukemias/lymphomas and related disorders are in the form of journals which list such cases by year of registration at the hematology departments or oncology dispensaries. Dr. Gudzenko has indicated that she will confirm that each such journal contains at a minimum the case's full name, gender, year of birth and diagnosis.

④ When choosing the random sample of retrospective cases with leukemias/lymphomas and related disorders the epidemiology group will strictly adhere to selecting the required number of cases in each disease sub-classification as determined by Drs. Finch, Dyaghil and Klimenko at the time of our meeting (see below).

⑤ At the direction of Drs. Finch, Dyaghil and Klimenko, the clinical records, peripheral blood and bone marrow or tissue sections will be requested for the following number of cases diagnosed within each disease sub-classification:

2 cases of chronic myelgenous leukemia
2 cases of chronic lymphoid leukemia
5 cases of acute leukemia
2 cases of leukemia related disorders such as myelodysplasia, myelofibrosis, polycythemia vera, thrombocythemia, etc.
3 cases of non-Hodgkin's lymphoma
2 cases of Hodgkin's disease
1 case of multiple myeloma
TOTAL: 17 cases

No more than 20 cases in total adhering to the categories described above will be chosen randomly from each of the six study areas (oblasts and city of Kiev) diagnosed within the period 1987 up to and including 1997.

The sample for review will be restricted to only males born between the years of 1946 and 1966 thus limiting the sample to the age group 40 to 60 years old at the time of the Chernobyl accident and therefore enabling us to focus on the confirmation of leukemias/lymphomas in adult males. We have chosen only males because Phase II of the study is restricted to male clean-up workers.

⑥ Details of the randomization process (as suggested by Dr. Howe) follows. The process should be based on a list for each oblast in which each entry on the list has a random year of diagnosis and a random page number. This list will be used to access the apparently sequential logs of cases maintained by each oblast oncology dispensary or hematologic department. Thus, to obtain a case of multiple myeloma one takes the first item on the list, goes to the log for that year and the page number for that year, then starts half way down the page and moves sequentially forward until identifying the first case with multiple myeloma satisfying the requirement that the case be male and born between 1946 and 1966.

⑦ Once the sample of cases with leukemias, lymphomas and related diseases has been made the appropriate staff at each participating oblast/city dispensary or oncologic clinic will be contacted by letter or telephone giving details of the material required for each identified case from that institution for the diagnostic review. At a minimum these include all clinical records (or summaries) including laboratory reports and any/all pre-treatment peripheral blood, bone marrow, and tissue sections or smears including cytochemical and other special stains.

NB It has been suggested that Dr. Dyaghil or a suitable delegate (possibly Dr. Robert Reiss) will visit each participating institution to review the material available for each case and suggest to the appropriate staff at the hospital when necessary any stains which should be re-stained at that institution. It is essential, of course, that the individual who participates in this exercise be excluded from participating on the review panel.

When asking the relevant institution for the required material on each case identified from that institution it is important to stress the need that they send to Kiev even the minimum clinical and biological material if that is all there is available for that case.

⑧ It should be explained to the appropriate staff at participating institutions that any costs incurred by sending material to Kiev for the diagnostic review will not be the responsibility of that institution. Appropriate logs of case material ascertainment, pick up/delivery to Kiev and return must be documented at all times.

G. Organization of Material Upon Receipt in Kiev:

① Wherever necessary, all material should be translated from Russian to English for the benefit of non-Russian speaking panel review members. If a French review member is included on the panel, it may be necessary to also translate material from Russian to French.

② Blinding of case material: On the advice of hematologists, wherever possible for all clinical and biological material for each case any information about that case which may lead to bias on the part of the diagnostic reviewer should be covered (with white sticky labels).

It has been suggested that Professor Burch and Dr. Gudzenko be responsible for the organization and direction of the review process. In this respect, Professor Burch's experience with a similar pathology review of brain tumors in an international study of such tumors in adults and children at the International Agency for Research on Cancer in 1997 should be invaluable.

H. The Diagnostic Review:

The actual process for the pathology review needs to be developed in collaboration with the hematologists and pathologists involved. However, the review should involve some measure of inter-reviewer variability and intra-reviewer variability (such as randomly including material from a single case twice in the review with the reviewer being ignorant of and blinded to this fact.)

The final objectives of the diagnostic review are: the review panel should be in agreement on terminology of classification; a determination of the quality of the clinical and histological material for making reliable diagnoses; and some determination regarding consensus opinions for the various diagnostic categories.

Dr. Stuart Finch has kindly suggested that the following guidelines be incorporated within the protocol and the review process:

① Completeness of information: For each case record presence or absence of (I) peripheral blood smear; (ii) bone marrow smear or section; (iii) tissue slide for lymphoma; and (iv) clinical record.

② Quality of information: Should determine whether histologic material submitted is or is not diagnostic relative to quality of histologic material (stein, smear or tissue thickness, labeling, appropriate sample, etc.) Also consider quality and completeness of clinical record information.

③ Diagnostic criteria: See protocol 8.2.2 on *certainty of diagnosis*, 8.2.3 on *acuteness of leukemia* and 8.2.4 on *certainty on type of leukemia*. Protocol guidelines may be modified to fit requirements for lymphoma.

④ Leukemia considerations should be:

- Acute vs. chronic;
- Acute lymphoid vs. acute non-lymphoid or uncertain type (FAB classification or unclassifiable);
- Other - myelodysplasia (FAB classification), myelofibrosis, aplastic anemia, etc. (see 8.1).

⑤ Leukemia information should include:

- certainty of diagnoses (definite, probable, possible)
- certainty of type of leukemia (definite, probable or possible)
- final diagnostic categories
- acute lymphocytic leukemia (FAB type or unclassifiable)
- chronic lymphocytic leukemia
- chronic myelogenous leukemia
- acute lymphocytic leukemia (FAB type or unclassifiable)
- acute myelocytic leukemia (FAB type or unclassifiable)
- unclassifiable acute leukemia (due to undifferentiation or other reason)
- myelodysplastic syndrome (FAB type)
- other type of leukemia
- leukemia related disorders (i.e., myelofibrosis, aplastic anemia, etc.)
- no diagnosis (incomplete or unsuitable material)
- not leukemia

⑥ Lymphoma information should include:

- certainty of diagnoses
- certainty of type
- final diagnostic categories
- Hodgkin's disease (histologic type)
- non-Hodgkin's lymphoma (NIH working formulation)
- other types of NHL
- unclassifiable (state reason)
- not lymphoma
- no diagnosis (incomplete or unsuitable material)

⑦ Epidemiologists summary of review should include a statement regarding lymphoma classification system agreed upon, a summary of all cases reviewed in accord with a - f above to include tabulations of the following:

- consensus agreement (or disagreement) on diagnosis of leukemia or lymphoma
- consensus agreement (or disagreement) on diagnosis of type of leukemia or lymphoma
- material determined to be unevaluable (poor records, poor or no slides, mislabeled, etc.)
- percent of original lists of leukemia and lymphoma cases confirmed by consensus as definite or probable.

NB However, before the final protocol for the review can be written it will be necessary for hematologists and pathologists in the Ukraine and United States to advise the epidemiology group (including Professor Burch) as to the appropriate procedural guidelines for the review.

I. Membership on the Review Panel:

The membership of the diagnostic review panel should be determined no later than the end of August 1998 so that the review can take place as soon as possible thereafter. It has been suggested that the review panel at the very least consist of one hematologist expert in leukemia morphology from both the Ukraine and USA , one hematopathologist expert in leukemias and lymphomas from both the Ukraine and USA and one hematologist/hematopathologist from France. It will be necessary to have one individual from each of the Ukraine and USA be responsible for the logistics of the review process. In this regard, as noted above, it has been suggested that Dr. Gudzenko and Professor Burch take this role respectively.

J. Time Frame:

It is anticipated that the epidemiology group in Kiev could have available to them the random sample of cases with leukemias, lymphomas and related diseases from the oblast/city hospitals by the end of August, 1998. Additionally, receipt of all clinical and/or biological material for the identified

cases could occur by the end of October with the organization of the material for the review process completed by the end of November/December 1998. The review process could then take place in Kiev in January of 1999. Dr. Finch estimates that the review process will require a time period of one week.

APPENDIX 3

Training Program for Dr. Sergey Sholom
at the University of Utah
July 11, 1998 to August 1, 1998

TRAINING PROGRAM FOR DR. SERGEY SHOLOM AT THE UNIVERSITY OF UTAH
JULY 11, 1998 TO AUGUST 1, 1998

Drs. Haskell, Chumak and Sholom had the opportunity of meeting in person at a recent EPR conference in Obninsk, Russia. During that meeting, they reviewed the protocol for Dr. Sholom's visit to the University of Utah and discussed other issues which might also be addressed during the visit concerning EPR dosimetry of tooth enamel.

On July 11, 1998, Dr. Sholom arrived in Salt Lake City and work has begun on sample preparation and preliminary EPR measurements.

The protocol for the three-week visit is as follows:

Three carious teeth and one tooth with no caries will be prepared and examined. All teeth will be Ukranian to eliminate possibilities of regional variations. For the non-carious tooth, the sample will be crushed to optimal grain sizes and enamel removed using a heavy liquid separation. Native signal data will then be obtained for the sample with associated sensitivity determinations following additive irradiations. Aliquots of these samples will then be treated with KOH to determine changes in native signal shapes and intensities along with sensitivity changes following additive irradiations. Sample mass dissolution rate will be monitored for comparison with that of the carious samples. For carious teeth, each sample will be cut into the following three general portions: 1) those portions appearing healthy and intact; 2) those portions that are carious and directly adjacent to carious decay; and 3) the intermediate regions between the first two that may or may not have visual discoloration. Each of the three portions of each tooth will then be crushed to optimal grain sizes followed by enamel separation via heavy liquid (we have verified that carious enamel can be removed in this way along with healthy enamel). Each carious tooth is then expected to have three aliquots of varying degrees of carious decay. Each aliquot will then be scanned for quantification of native signal shape and intensity. This will be followed by additive irradiations to determine aliquot sensitivity. Each sample will then be treated in KOH to be followed by EPR scanning to assess induced changes in native signal intensities and with more additive irradiations, sensitivity changes.

APPENDIX 4

Proposal for Training of Chernobyl Project Staff
Ukraine Thyroid Project

PROPOSAL FOR TRAINING OF CHERNOBYL PROJECT STAFF
UKRAINE THYROID PROJECT DCC

Daniel F. Heitjan, PhD

Proposed trainee:
Vyacheslav (Slava) Derzhovets, head of the Kiev Thyroid DCC.

Dates of visit:
July 3 to August 20, 1999 (second session of Columbia SPH summer semester).

Courses:
Intro. to Biostatical Methods (Columbia P6104)
SAS Fundamentals: A Programming Approach (SAS Institute)

Practicum:
Participate in the data management and statistical analysis of an ongoing clinical trial or epidemiologic study.

Office & Computer:
The Division of Biostatistics can provide a desk. The project will supply a laptop computer.

Costs (exclusive of travel and living expenses):

Columbia tuition (projected)	$2,980
SAS tuition (projected)	800
Books, course materials, supplies	500
Laptop computer	2,200
Total	$6,480

Courses and locations:

"Biostatistics P6104" is a 45-hour core course on biostatistical design and analysis. It normally takes all semester but in the summer we offer it over six weeks.

"SAS Fundamentals: A Programming Approach" is a basic course in SAS programming for users who already have some programming experience. SAS Institute offers this three-day course every month at their New York training facility on 7th Avenue in Midtown.

Gil Beebe had suggested sending Slava to the Johns Hopkins summer school in Baltimore, but I think it is better, for a number of reasons, for Slava to come to New York. Our course is longer and more expensive, but I suspect that with his meager English, Slava will need more time to get started and actually learn something. Moreover, the SAS course, which is really essential, is not offered in Baltimore. Presumably Slava will also feel more comfortable in New York, where we have Russians on staff and a large Russian population nearby. Most importantly, it will give us the chance to work together and have regular discussions of the project.

Justification of laptop computer purchase:

I suggest that the project purchase a laptop computer for Slava's use during his visit. His courses and practicum will all require computing, so it makes sense to have a dedicated machine available from day one. When his visit is over, we can either send it back with him or keep it for our own travels and for future trainees.

Practicum:

APPENDIX 5

Review
Radiation-Induced Breakpoints in Human Chromosomes: Random or Non-Random?

Review

Radiation-induced breakpoints in human chromosomes: random or non-random?

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Abstract

Whether radiation-induced chromosome breakpoints are randomly or non-randomly distributed throughout the human genome remains unclear. This question has important implications for the use of cytogenetic analysis for biodosimetry purposes and also addresses the effect of mechanistic influences on breakpoint localization. In this review, we combine data from as many cytogenetic studies as possible and determine the percentage of radiation-induced misrejoined breaks per megabase (Mb) of DNA occurring between chromosomes of the human genome. We also compare the observed and expected number of breakpoints based on DNA content between and within chromosomes. The results show a DNA-proportional distribution of breakpoints in 14 autosomes and a statistically significant deviation from proportionality in the other 8 autosomes and the sex chromosomes. Regression analysis shows no significant change in breakpoint frequency per Mb DNA relative to autosome size in the combined studies. These results indicate that there is an approximately linear proportionality between DNA content and observed breakpoint number, supporting the conclusion that subsets of autosomes can be used to estimate accurately the overall genomic frequency of misrejoined breakpoints contingent upon a carefully selected subset. However, this conclusion cannot be applied to the sex chromosomes. The results of the analysis between chromosome arms show a non-random distribution of induced breakpoints within certain autosomes, particularly the acrocentrics. In all cases of significant deviation from a random intra-chromosomal inter-arm

distribution, a prevalence of events was found at heterochromatic regions and/or telomeres. In addition, a clustering of breakpoints was found near the centromeres of many chromosomes. These results further support the influence of chromatin organization and/or preferential DNA repair/misrejoining on the distribution of induced breakpoints. However, these effects are not sufficient at a global level to dismiss the value of cytogenetic analysis using a genome subset for biodosimetry.